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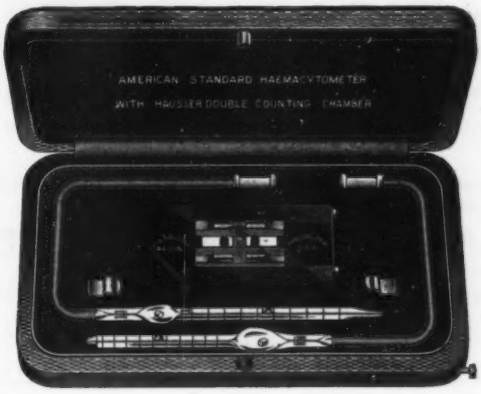

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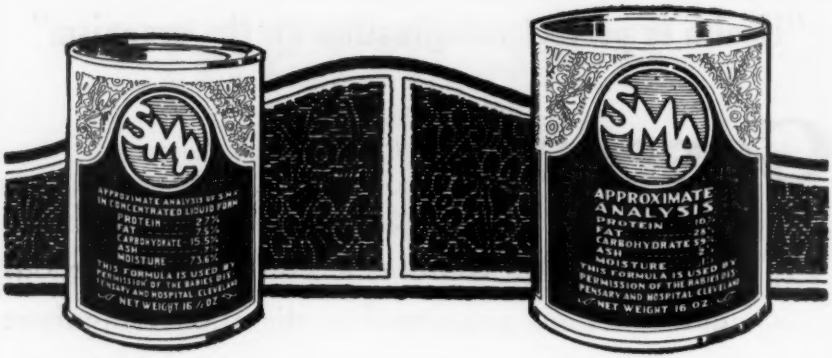

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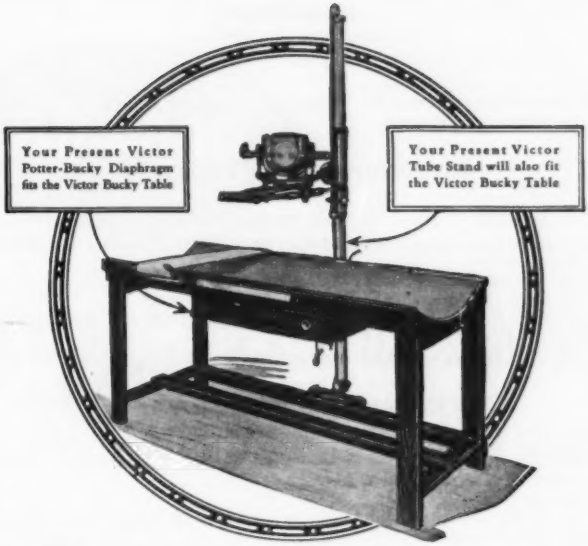
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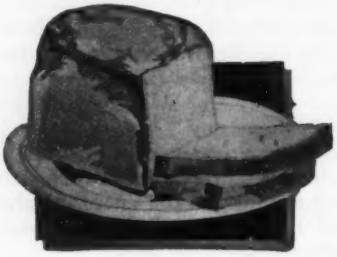

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AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JULY, 1922

ORIGINAL ARTICLES.

THE ACTIONS OF ATROPINE AND QUINIDINE IN FIBRILLATION OF THE AURICLES; CLINICAL AND EXPERIMENTAL STUDIES.

SECOND LECTURE*

By Thomas Lewis,

UNIVERSITY COLLEGE HOSPITAL, LONDON, ENGLAND.

In studying the action of quinidine upon the fibrillating auricle and in considering the nature of this action, we may conveniently begin by noticing certain effects of vagal stimulation, and certain effects of abolishing vagal tone, upon the mammalian auricle.

For many years it has been customary to regard an increased vagal tone as having a purely depressant effect upon the functions of the mammalian heart muscle. We know that vagal stimulation slows the natural heart beat, produces heart-block at the *A-V* ring, that it notably reduces the force of the auricular contractions and that, under vagal stimulation, the auricle will no longer respond to electric shocks of previously threshold strength. From these observations it has been natural to conclude that the vagus tends to inhibit rhythmic impulse formation in the heart, that it hinders

* Observations carried out on behalf of the British Medical Research Council at University College Hospital Medical School (London). A Wiley-Noble-Jones Lecture, delivered at the University of Oregon Medical School, Portland, in May, 1922. In this lecture I have utilized much material, as yet unpublished in detail and collected in collaboration with my coworkers, Dr. A. N. Drury, Dr. C. C. Iliescu and Dr. A. M. Wedd.

The third and last lecture will appear in the August issue of this publication; the first lecture appeared in the June issue.

conduction in the heart, and that it reduces the force of the muscular contractions and decreases the excitability of the muscle. We have been tempted to apply all these conclusions to the muscle of the heart generally, and especially to the auricle, in considering the action of the vagus upon forms of auricular disorder. If we are to avoid serious fallacy, we must particularize and avoid transferring a conclusion which applies to one section of heart muscle to a second section. Since vagal stimulation reduces the power of the *A-V* tissues to conduct in the mammalian heart, there would seemingly be little risk in concluding that its action is similar upon the muscle of the auricle itself, for this muscle is known to be powerfully controlled by the inhibitory nerve. But the risk of such conclusions is a grave one, as this example illustrates; recent observation has shown quite clearly that the vagus has not the power to depress auricular conduction. If the mammalian auricle is beating normally, vagal stimulation leaves conduction in this muscle unchanged. Furthermore, if for any reason the rate of conduction is primarily reduced in the auricle, then vagal stimulation exerts a paradoxical effect; it increases the rate of conduction. For the purposes of this lecture we are concerned chiefly with depressed conduction due to an increased rate of beating, such as occurs in flutter and in fibrillation; in the case of conduction slowed by this cause, vagal stimulation brings transmission rates back to normal.[8] The meaning of this becomes clearer if we recognize that this disturbed conduction is connected with the refractory period of the muscle under observation. If a new stimulus falls on the muscle before it has obtained sufficient rest, it finds this muscle only partially recovered; it is partially refractory, and the wave propagated therefore travels slowly. When the vagus is stimulated, the contraction of the muscle is much reduced in amplitude, it is also conspicuously reduced in its duration;[8] the systoles are now very brief and the rest periods between the responses become sufficiently prolonged to permit complete recovery.

Thus, from recent observation come two conclusions: Vagal stimulation (1) conspicuously reduces the length of the refractory period and (2) it quickens conduction in an auricle which is beating rapidly. Section of the vagi, or atropinization,[8 11] have the opposite effects. These two conclusions are of much consequence when we consider the effects of vagal stimulation upon the fluttering or fibrillating auricle.

Our reasons for the belief that auricular flutter and fibrillation are dependent upon a circus movement have been discussed at some length,* and for the purposes of this lecture I ask you to accept this conclusion. The maintenance of a circus movement in the auricle

* The nature of flutter and fibrillation was the theme in two preliminary lectures of this series, the ground covered being very similar to that covered by the Oliver-Sharpey lectures[6] of 1921.

depends on certain factors which we may now examine in some detail.

It is essential that as the wave circulates, a gap between its crest and wake should be maintained. Otherwise the crest of the wave, in advancing, will find no responsive muscle ahead of its movement. Upon the existence of this gap, the maintenance of the movement depends absolutely.

The Length of Gap. Start a wave in one direction along a circular path. The wave begins at one point, and moves around the circle. The muscle at the starting point becomes refractory or unresponsive as it receives the wave; it remains unresponsive for a given length of time, a period termed the *refractory period.*

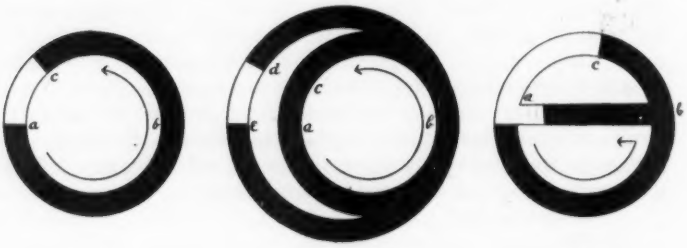
The shorter this refractory period, the smaller will be the distance which the wave travels before the starting point again enters the responsive state. The shorter the distance travelled by the wave in a given time, the greater will be the gap left between its crest and the starting point to which it is returning. The distance travelled will be less, the slower the wave moves; a longer gap results therefore from slower conduction. Finally, the longer the path to be travelled by the wave, the longer will be the gap. Thus, the length of gap is determined by three factors:

1. Length of path.
2. Duration of refractory period.
3. Rate of propagation.

Although these three factors obviously *determine* the length of the gap, strictly speaking it is not correct to say that they all control it. The original muscle tract persists unaltered and, so long as the state of conduction and refractory period remain unchanged, the wave will move along it. It is change in one of the last two factors, which can alone alter the original gap. Refractory period and conduction rate alone *control* the gap. But, subject to change in one or other of these factors, the path itself may vary.

This variation is brought about in the following way. Suppose that the refractory period lengthens or the rate of propagation increases, the gap shortens. If from either of these causes the gap *disappears,* the wave does not necessarily cease to circulate; it will continue to circulate if a longer channel is open to it (Fig. 1 *b*). Reversely, if the refractory period shortens, or the rate of propagation decreases, the gap will widen and, in widening, it may open up to the wave a shorter channel, which the wave will then pursue (Fig. 1 *c*). The moment lengthening or shortening of the path occurs, this change will also affect the length of gap; but it is to be emphasized that this change is secondary to change in the remaining factors and consequently becomes of secondary importance theoretically, when changes in the gap are considered. These remarks bring me to discuss our problem in a different manner.

The Number of Circuits per Minute. As the wave is continuous, the number of circuits per minute depends solely upon the circulation time. It will be at once evident that the time of circulation is determined by the length of the path and the rate at which the wave travels; refractory period exerts no direct influence. The circulation time will be shorter, and the circuit movements will be more numerous if the path is short and the rate of propagation rapid; conversely, the time will be longer, and the circuit movements fewer, if the path is long and the rate of propagation slow. But refractory period cannot be left out of the account, it is subject to variation; by increasing it can force the wave to travel upon a longer channel, by decreasing it can induce the wave to flow upon



A. B. C.

FIG. 1. A.—A diagram of a wave circulating in a ring of muscle. The wave travels in the direction *a*, *b*, *c*. *c* represents the crest of the wave and *a* represents its wake; these travel at the same rate and leave between them a constant gap of responsive muscle *ca*. The muscle which is refractory, *i. e.* in a state of contraction, is represented black. Suppose now that the refractory period suddenly lengthens; the muscle at *a* will remain refractory for a longer time and, as the crest *c* is all the time advancing, the gap *c a* will tend to close. If it closes, the circus movement on the original path (*abc*) will be brought to an end (Fig. 1 B); but the circus movement may itself continue if a new and longer channel (*d e*) is open to it (Fig. 1 B). Similarly if, while the conditions are those of Fig. 1 A and the refractory period suddenly shortens, the gap will increase in size. This increase in the length of the gap may open up a new channel (*b a* in Fig. 1 C) upon which the wave is now able to circulate.

a shorter channel. Variations in the length of the path are controlled by the dominant factors, refractory period and rate of conduction. It is to these two that we constantly return, from whichever standpoint we regard the wave. The length of path becomes a secondary consideration. A shorter circulation time, an increase in the number of circuit movements per minute is induced: (*a*) By an increased rate of conduction and (*b*) by a decrease in the refractory period when this permits the wave to accept a shorter path. Conversely a decrease in the number of circuit movements per minute is induced: (*c*) By a decreased rate of conduction and (*d*) by an increase in the refractory period when this forces the wave into a longer channel.

These are the broad effects, though the question is a complex

one. An increase or decrease in the rate of conduction will be mainly, perhaps solely, effective when the original gap is a material one. An increase or decrease in the refractory period will be mainly or solely effective, when the original gap is small and the wave is free, at the change, to take a shorter or longer channel.

The path may also change, theoretically, as a result of change in the rate of conduction. If this occurs, the effect of the secondary change would tend to neutralize the effect of the primary change, so far as an influence on rate of circulation is concerned. It is even conceivable that a decreased rate of conduction might lead, by materially shortening the path, to a decrease in circulation time (or an increase of the first to an increase of the second); but these paradoxical effects could only occur in very special circumstances. It is here to be remarked that probably in auricular muscle beating at a high rate, change in conduction and in the refractory period never occur apart from one another. Slow conduction appears always to be associated with lengthened refractory period; at all events this is so far as the variations described in the present lecture are concerned. These two changes, acting in concert, but in opposite directions so far as they influence the length of path, tend to neutralize each other.

The Action of the Vagus. Consider the action of the vagus, in the light of this theory of circuit movement: by reducing the transmission time it will expedite the circus movements; if, by reducing the refractory period, it reduces the length of path, the reaction will be in the same direction. Thus, vagal stimulation should accelerate the movements of the auricle in flutter and in fibrillation. It is well known to do so in experiment.[9] [12] Clinically it is difficult to obtain a sufficiently powerful stimulation and, as a rule, little change of auricular rate is to be observed; thus, in recent attempts to alter the rate of the fluttering auricle by vagus pressure we have failed, neither can we detect the slightest change of rate in past records of this kind; in this connection it is interesting to observe that Levine and Frothingham[5] noted a slight change of rate in deep respiration, and the *relation* was the reverse of the normal; the increase of rate was seen during expiration, an act which exalts vagal tone. The direction in which they observed change is the direction which our theory would predict.

The Action of Atropine. The effects of atropine are the reverse of those of vagal stimulation. Thus in experiment, atropine increases the transmission intervals in the rapidly beating auricle;[11] it tends to prolong the refractory period.[8] Atropine, therefore, should slow the rate of auricular movement in the fibrillating auricle. This effect is actually witnessed in experiment.

The fall of rate where atropine is injected into patients who are the subjects of this disordered heart action is perhaps not absolutely constant, but usually the effect is definite and may be

conspicuous, in some cases it is very conspicuous, the auricular rate falling often 50, sometimes even 100 or 150 beats per minute (Fig. 2).

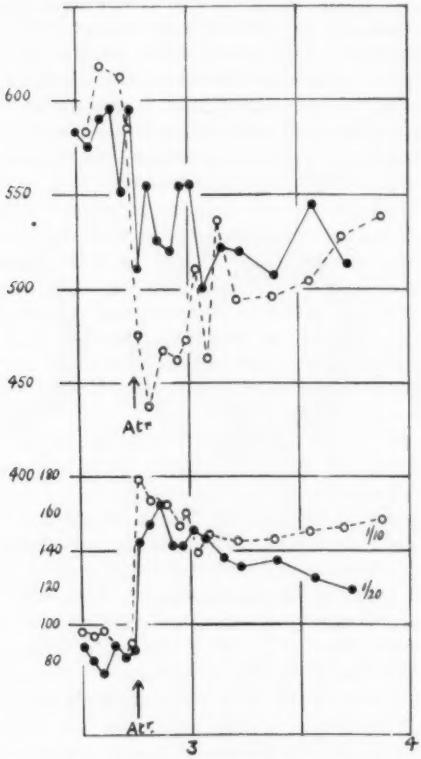


FIG. 2.—A chart from a case of fibrillation of the auricles, showing the effect of injecting $\frac{1}{20}$ and $\frac{1}{10}$ of a grain of atropine intravenously. The ventricular rate (lower curves) rises; the auricular rate (upper curves) falls. In these instances the falls of auricular rate are unusually conspicuous. Note that the reaction to $\frac{1}{10}$ is greater than to $\frac{1}{20}$ of a grain of atropine.

The Action of Quinidine. In considering the action of quinidine upon auricular fibrillation, we have to consider separately its action upon the auricle and its action upon the ventricle. These will be taken separately. Clinically two actions upon the auricle are witnessed, the first of which, namely, slowing of the auricular movements, is constant; the second of which, namely, restoration of the normal rhythm, is inconstant, occurring in about 50 per cent of our cases.

Action of Quinidine in Slowing the Auricle. When quinidine is given to dogs in similar doses per kilogram of body weight to those used therapeutically, among other reactions two stand out from our present point of view. Quinidine conspicuously lengthens the refractory period of the auricle; it lengthens this period 50 to 100 per cent. Its action in this respect is the most powerful known to be produced by therapeutic doses of any drug now used in cardiac maladies. The drug has a further action: it slows conduction in the auricular wall; the transmission intervals widen out; the increase is variable, but is usually from 50 to 100 per cent.[11]

Lengthened transmission intervals, according to the theory of circus movement, would profoundly slow the auricular rate. The longer refractory period of the muscle, if it exerted an influence upon rate, would act in the same direction; for if sufficiently prolonged it would divert the wave upon a longer path. Reflection will show that an equal percentage increase in refractory period and conduction time, would leave the wave in the same path, would leave the gap unaltered, but would double the time of its circulation and halve the number of circuits completed. Only when the effect on the refractory period outweighed that on conduction, would the path tend to lengthen. Thus, knowing the effects of quinidine upon auricular muscle, we are able to anticipate its influence on the rate at which the fibrillating auricle beats. It should produce, it does actually and invariably produce, profound slowing.

Thus, the effects of vagal stimulation, of atropine and of quinidine upon the rate of the fibrillating auricle, are clearly explained, if we accept as the basis of our argument, circus movement as the underlying cause of fibrillation.

Restoration of the Normal Rhythm. Theoretically, the normal rhythm can be restored in flutter or fibrillation, by closure of the gap between the crest and wake of the circulating wave, and by this means only; for the movement should continue so long as this gap of responsive muscle exists.

What factors will tend to close this gap so that it cannot reopen? The gap will shorten and tend to close if one of the following events happen alone:

1. An increased duration of the refractory period.
2. An increased rate of conduction.
3. A shortening of the path.

The last we need not consider, for actual and final closure would not occur so long as the longer original path remained open as an optional channel. Further, we need not consider an increase in the rate of conduction, for under quinidine, the reverse happens. Closure of the gap and the ending of circus movement would however receive an adequate explanation from lengthening of the refractory period. But fibrillation is not always terminated by

the administration of quinidine; it is not to be expected, since quinidine also slows conduction. The widened refractory period tends to close, the slowed conduction tends to open the gap; and it is only when the first effect exceeds the last that closure is to be anticipated. There is another reason why fibrillation should not always terminate under quinidine. Closure of the original gap may divert the circus movement along a longer path. A further increase in the refractory period might then prove effective, or it might not; the end result would depend on the extent of the longest available path.

It is evident that, knowing the effects of quinidine upon the muscle, and applying this knowledge to the theory of circus movement, we might anticipate the actual end results which are witnessed. Abrupt termination of the disorder in one case, failure to terminate in another.

Before leaving these effects of quinidine upon the auricular disorder, it is to be noted that quinidine does not act on the muscle alone; it also acts on the vagus. Its effect is to paralyze this nerve partly or completely. The manner of its action is not the same as that of atropine, for atropine acts on the nerve endings, while quinidine would appear to act, according to Dale's recent observations,[1] upon the nerve ganglia; the end result, so far as we are now concerned, is the same. Vagal tone decreases. Fortunately for our theoretical consideration, this change in nerve control acts in the same directions as do the direct effects on the muscle, a fact which is expressed correspondingly in the accompanying table.

TABLE.

	Refractory period.	Transmission time.	Rate of auricular movement.
Vagal stimulation	−	−	+
Atropine	+	+	−
Quinidine (direct action)	+	+	−
Quinidine (indirect action)	+	+	

Since both the direct and indirect action of quinidine are similar in end-results to those of atropine, it may be asked why the last drug is not capable of bringing fibrillation to an end. The reply is that in some circumstances it does do so; for the fibrillating auricle of the dog, atropine is usually an effective remedy,[7 14] stopping the disorder immediately. It is clear however that it is not effective clinically in chronic cases of fibrillation; though it might be so in more acute cases. A statement has been made that Hering[3] saw fibrillation abolished by atropine in man. This does not appear to have been so, the case being a disorderly rhythm of a different kind, as Hering[4] has stated. In patients, fibrillation is more firmly rooted than in dogs in which it has been produced by stimulation; and atropine, though it acts in the same directions as quinidine, has a far less powerful action.

It may be of interest to note that our observations upon atropine preceded our personal acquaintanceship with quinidine and its use in fibrillation.

The effect of Quinidine on the ventricles in fibrillation of the auricles is a complex one. In chronic fibrillation, a rise of ventricular rate is almost constant and is usually conspicuous. The rise coincides with the fall of auricular rate when single doses of the drug are given; using repeated doses, the ventricular rate often tends to fall away, although the auricular rate still remains low. Three factors appear to be involved, namely, the fall of auricular rate, loss of vagal tone and a direct action of quinidine on the conducting tissues. We may consider these separately.

When the auricle is beating rapidly and the ventricle is failing to respond to all the impulses so created, a fall of auricular rate tends to raise the rate of the ventricle. That is so because, as is well known, the degree of block becomes less as the auricular rate falls. In treating patients with quinidine this reaction is sometimes shown, unequivocally; thus sometimes, if the auricular rate is driven down to the neighborhood of 200 beats per minute, the ventricle, which previously responded to each second beat of the auricle, suddenly assumes the full auricular rate; there is an abrupt rise of ventricular rate to approximately double its former level. Such an abrupt rise can have but one meaning, it is a pure response to the events in the auricle. When, however, we deal with the more gradual rise in the earlier stages of administration, it is less easy to estimate accurately the part played by auricular rate, though we may be sure that this influence is exerted. Its degree is difficult to estimate because we must presume that vagal tone may also be changing.

To what extent are the vagi paralyzed by quinidine, given in therapeutic doses? If the action is comparable to that witnessed in experiment the paralysis should be considerable. Yet it can be shown that this is not the case, for if a single dose of quinidine is given, amounting to 0.6 or 0.8 gm., then an injection of atropine at the height of the quinidine reaction lifts the ventricular rate very appreciably (Fig. 3). Moreover, the rate, to which the ventricle can be forced by atropine alone, is a good deal higher than that which is attained under quinidine (Fig. 4), except in those cases in which the auricular rate falls so low that the ventricle attains the full auricular rate. The vagal paralysis produced clinically is at the most only partial. But the *number of beats* by which the ventricular rate rises, is greater when atropine is given alone than when atropine is given to a patient in whom the ventricular rate is already raised by quinidine (Fig. 4). This indicates that paresis of the vagus does play a part, though the degree in which this factor participates appears to be variable. An action upon the vagi as powerful as that seen in experiment is improbable,

since in the case of dogs the alkaloid is given intravenously and in man it is given by the mouth.

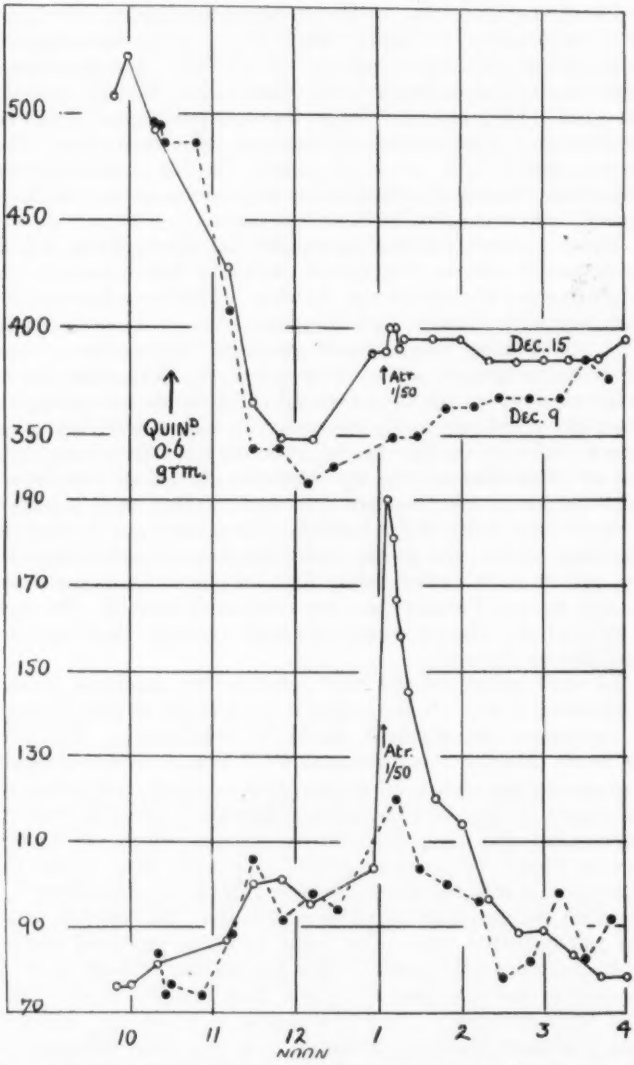


FIG. 3.—A chart from a case of auricular fibrillation, comparing the effect of a single dose of 0.6 gram of quinidine (black circles) with a similar dose of quinidine to which an intravenous dose of atropine has been added (plain circles). To show that the vagi are not paralyzed by the quinidine.

In experiments upon animals, almost all workers have noted that quinidine depresses conduction at the *A-V* junction. [2 11 13]

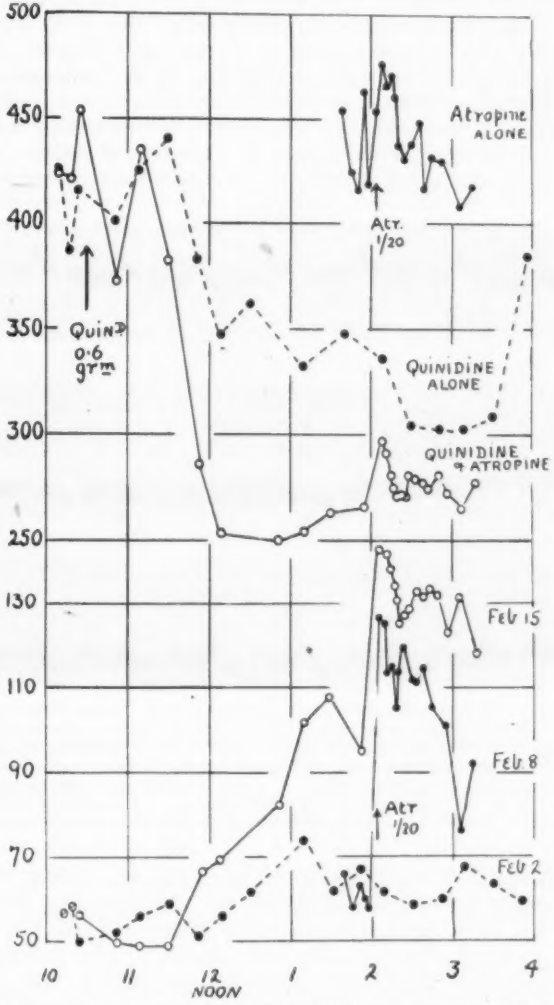


FIG. 4.—A chart from a case of auricular fibrillation, comparing the effect of (a) a single dose (0.6 gram) of quinidine (black circles, and broken line), of (b) a similar dose of quinidine to which an intravenous injection of atropine has been added (plain circles) and of (c) an injection of atropine alone) black circles and unbroken line).

This is more notable if the auricular rate is artificially maintained at a high level. It is due to a direct action on the muscle, for

atropine or vagal section does not affect it. Such an effect, if it exists in man, must influence the ventricle in the reverse direction to that so far discussed. Now this effect does exist in man, for in most instances where there is a sudden resumption of the normal rhythm the *P-R* interval is seen to be prolonged (Fig. 5); and this prolongation is clearly due to quinidine, for it disappears during the following twenty-four hours, if the administration of the drug is brought to an end. To what extent this controlling action upon the ventricle is exerted during the treatment of patients with quinidine it is not as yet possible to say; many more observations

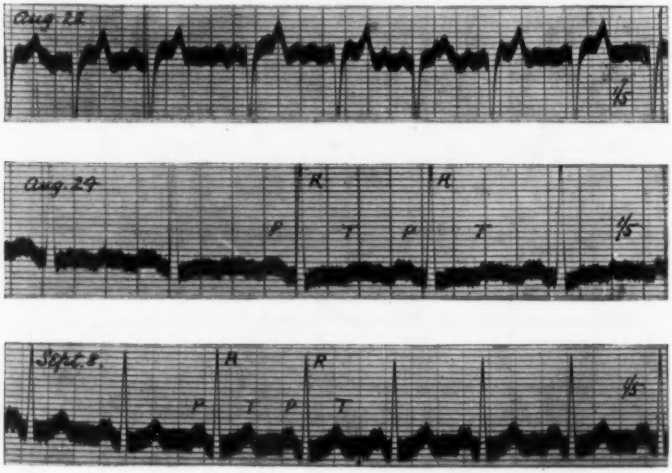


FIG. 5.—Three curves taken from a patient suffering from chronic fibrillation of the auricle. The first curve, which was taken by a direct lead from the chest wall, illustrates the fibrillation and was taken on the 22d of August. Quinidine was given amounting to 2.4 grams in two days. The normal rhythm became restored on the 24th of August. The second and third curves are from lead II and show this normal rhythm on the day of its restoration and a fortnight later. Immediately after its restoration the *P–R* interval is a little prolonged; the *T* wave is temporarily inverted.

are required before this question can be regarded as settled. The only indication of its influence during the administration of the alkaloid and while the auricles are still fibrillating is found in the tendency in many cases for the ventricular rate to fall when treatment is prolonged, a tendency otherwise unexplained. It would seem from this observation that the action comes into appreciable play only in the later stages of treatment, when the amount of quinidine in the body is at a maximum.

The Theoretical Importance of Quinidine Reactions. In my previous lecture I have indicated that I regard the reactions of clinical fibrillation to quinidine so far discovered as of more theoretical

than of practical importance. In the present lecture, I have tried to show that quinidine reactions, notable as they are, are to be explained if we assume that we are dealing with auricles in which circus movements have become established. The way in which observations and theory harmonize is, I think, sufficiently remarkable; this accord affords strong circumstantial evidence that the theory of circus movement is sound. The reactions of the heart to quinidine test a theory which, if true, is of fundamental consequence to our conceptions of disordered rhythm. They are severe tests; nevertheless, the theory still holds good. Let the final verdict in regard to the usefulness of quinidine in therapeutics be what it will, and the outlook is by no means unhopeful, the new knowledge gained from its reactions, the new lines of research which they have suggested and will continue to suggest, are far from negligible. Quinidine is not only testing new current theories,

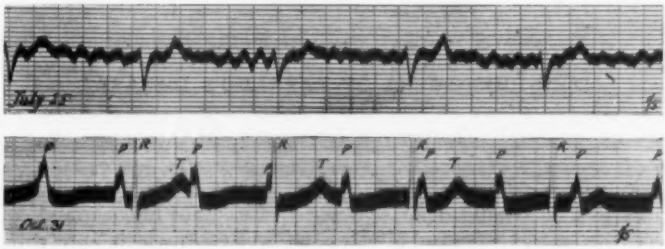


FIG. 6.—The upper is a curve taken on July 25 by leads from the chest wall. It shows fibrillation of the auricles and a slow and regular action of the ventricle. A single dose (0.6 of a gram) of hydroquinidine was given on October 31 and this restored the natural action of the auricle (lower curve). The mechanism is now one of complete heart-block; this continued unaltered.

but it is bringing valuable confirmation of older conclusions. One of the most striking of these is its final proof that fibrillation and flutter are fundamentally similar. Another incidental service which it is accomplishing, is that it is confirming the analysis of those cases of fibrillation in which the ventricle beats slowly. These cases have been interpreted as instances of combined fibrillation and heart-block; quinidine clearly displays this block when it restores the normal rhythm (Fig. 6). Recently we have treated a case of fibrillation in which the ventricle beat constantly and slowly at 30 to 40 per minute; when the auricle resumed its natural beat, complete block was disclosed. Quinidine will continue to bring knowledge of this kind; it is opening up many lines of original research.

If the theory of circus movement is finally accepted, careful research upon quinidine will continue to throw light upon the precise factors involved in the maintenance of this movement;

it has yet to guide us further in arriving at a clearer idea of the real distinction between the two closely allied conditions, fibrillation and flutter.

REFERENCES.

1. Dale: Heart, 1921, **9**, 87–89.
2. Hecht and Rothberger: Ztschr. f. d. ges. exper. Med., 1918, **7**, 138.
3. Hering: Deutsch. Arch. f. klin. Med., 1908, **94**, 185.
4. Hering: München. med. Wchnschr., 1909, **56**, 2483.
5. Levine and Frothingham: Archiv. Int. Med., 1916, **16**, 818.
6. Lewis: Brit. Med. Jour., April 16 and 23, 1921.
7. Lewis and Cotton: Heart, 1921, **8**, 37.
8. Lewis, Drury and Bulger: Heart, 1921, **8**, 83.
9. Lewis, Drury and Bulger: Heart, 1921, **8**, 141.
10. Lewis, Drury and Iliescu: Brit. Med. Jour., 1921, **2**, 515.
11. Lewis, Drury, Iliescu and Wedd: Heart, 1921, **9**, 55.
12. Rothberger and Winterberg: Archiv. f. d. ges. Physiol., 1914, **160**, 42.
13. Schott: Deutsch. Archiv. f. klin. Med., 1920, **134**, 208.
14. Winterberg: Archiv f. d. ges. Physiol., 1908, **122**, 361; (see also Rothberger and Winterberg, ibid., 1910, **131**, 387).

THE PHENOMENA OF RAYNAUD'S DISEASE.*

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In 1862, Raynaud reported a series of cases of his own and collected from the literature another series of cases which "presented very unusual features on the part of the vascular apparatus." In 1874, Raynaud contributed a final article on the same subject, and following this, publications became voluminous in every country in the world. In the course of time stress was placed on phases of the phenomena which were not a necessary part of the picture, and some of the essential features were obscured. The phenomena are usually spoken of as "Raynaud's disease."

The symptoms manifested in Raynaud's disease are attributed to a disturbance of the vasomotor apparatus. Vasodilation was first observed by Claude Bernard, in 1851, following section of the cervical sympathetic nerve. He was so impressed by the heat of the rabbit's ear that he mistook the cervical sympathetic for a thermal nerve. This misconception was corrected by Brown-Séquard, who after sectioning the cervical sympathetic nerve stimulated the peripheral end. Constriction of the bloodvessels resulted. He interpreted this finding to mean that the cervical sympathetic nerve possessed primarily dilator and constrictor powers. In 1887, Heger demonstrated afferent vascular nerves which acted reflexly to produce dilation and constriction of the bloodvessels in general.

* This work was done in the Section on Neurology, Mayo Clinic.

A controlling center for the vasomotor apparatus has long been considered a fundamental part of the mechanism, but the work of Porter and Hunt has shown that there are two centers, one related to the vascular dilator activities, the other being vasotonic or constrictor. The vasoconstrictor center has been located in the gray matter of the medulla with transfer centers in the gray matter of the spinal cord. The vasodilator center has not been located.

The response of vasomotor fibers to stimulation has been studied by Porter and Turner, Hunt, Gruber, Martin, Gunning and many others. The vasomotor center has been subjected to careful investigation, from the standpoint of pharmacology, by Pilcher and Sollman. In all of the studies attention has been paid chiefly to the general effects of vasomotor stimulation or depression. The significance of these studies has been briefly summarized by Brown. As the local effects of a disturbance of the vasomotor apparatus are confined to constrictor and dilator manifestations with their concomitant signs, it is very difficult to reproduce in animals experimental phenomena similar to those observed in man. The most important experimental work has been carried out by Krogh, whose work has been recently reviewed by Policard. In man the local manifestations of a disturbance of the vasomotor apparatus are most apparent in the series of phenomena associated with the vascular apparatus, which are seen in Raynaud's disease. The local manifestations can be grouped under (1) changes in color and nutrition, (2) changes in sensation, (3) changes in the motor system, and (4) changes in the bones.

Changes in Color and Nutrition. These changes may be discussed under four main divisions, white, blue, red and black.

White. The term "local syncope" was introduced into medical literature by Raynaud to signify the sudden blanching of a part of the body. It is the primary stage of the phenomenon known as Raynaud's disease. It is the most frequent expression of a disturbance of the vasomotor mechanism and is entirely compatible with good health. It is rare, according to Osler, in any disease except in the syndrome described by Raynaud. Oppenheim has observed it, in addition to the Raynaud type of disease, in healthy neuropathic persons, in anemic persons or in persons with disease of the kidneys, and never accompanied by any further symptoms.

Local syncope expresses itself in a fairly characteristic manner. The affected part suddenly turns surprisingly white and cold. The part has the appearance of death. The color may be white with greenish tone, or with bright blue or bright red tinges. During the continuation of this phenomenon the temperature may be depressed, and often is, from 15° to 20°. The condition lasts for from a few minutes to a few hours. In the cases comprising this study the time varied from fifteen minutes to one hour. Osler has observed sweating of the part during the attack. If it

persists too long, gangrene may supervene. This phenomenon was well illustrated by Raynaud's first case. The patient, a woman, aged twenty-six years, had had symptoms in her fingers and toes since childhood. In moderately cold weather, and even in the height of summer, her fingers and toes became exsanguinated, completely insensible, and of a whitish-yellow color. The attacks came on without apparent cause and terminated by a period of painful reaction. She was always free from attacks during pregnancy. A very typical example of this manifestation was observed in the Mayo Clinic in the latter part of 1920. A married woman (Case 339485), aged fifty-two years, had had peculiar symptoms in her fingers and later also in her toes for the last twenty-three years. The trouble came on suddenly and continued without intermission. All the fingers of both hands to the metacarpophalangeal knuckles suddenly turned white with a clear line of demarcation. The pallor was associated with a tingling sensation. The attack was always brought on by cold, such as dipping the hands in cold water, going from a warm room into a cold room or going out of the house into the outside air during cool weather. The attack lasted for from fifteen minutes to two and one-half hours. Otherwise her health was good. The patient's son had the same difficulty.

Blue. In order to distinguish the periodic attacks of blueness in various parts of the body, Boyer introduced into medical literature the term "local asphyxia." Raynaud applied this term to the second stage of the phenomena observed by himself. The blueness, characteristic of local asphyxia, may be bluish white or violet-gray, or there may be redness with varying degrees of blueness. The blueness disappears on pressure, with an abnormally long interval before the return of normal or of the bluish coloration. There may be marbling of the affected part, consisting of blue rings with pale centers. There is a slight diminution of the local temperature, but much less than that observed during local syncope. There are frequent sudden changes of color. Often the affected part swells temporarily or sweats, making the part cold and clammy. If the local asphyxia persists, as it may, for years, a sort of false edema results, owing to the excessive predominance of cellulo-adipose tissue brought about by undernutrition. This phase of the phenomena of Raynaud's disease is the most inconveniencing, as it renders life miserable to the patient because of the pain which is so commonly associated with it. Local asphyxia and local syncope may succeed one another rapidly, and may appear as constantly interchanging processes; local asphyxia is usually of longer duration than local syncope. Solis-Cohen spoke of these rapid changes as vasomotor ataxia. Gangrene is produced by too long persistence of local asphyxia. Local asphyxia, like local syncope, is paroxysmal, and recurrent, and may be symmetric or asymmetric. It is

more painful than syncope. Often the epidermis desquamates after an attack. In some cases the symptoms occur regularly at a certain hour, and with each new attack the severity of the cycle increases. The attacks finally disappear by a gradual daily decline of severity of symptoms.

The usual course of local asphyxia was typified in a patient (Case 231824), who visited the Clinic in 1918 on account of a peculiar trouble in the legs. One and one-half years before she suddenly developed cyanosis and very slight edema in the left leg. The cyanosis came on when she was exposed to cold or when she was walking. Six months later she developed similar trouble in the right leg, and still more recently her hands became involved. During the attacks menstruation was suppressed, often as long as two months; when the attacks subsided it was established. Her finger nails and one great toe nail dropped off without any apparent cause. November 15, 1920, she was improved, but still having trouble, especially when walking.

In Raynaud's series of cases under the heading of local asphyxia a patient was described who, when exposed to the cold, had marked cyanosis of the nose, chin, cheeks, hands and feet. The phenomena were first a paling, then a violet or slaty-white tint and later a deep purple. The discoloration faded quickly with warm applications.

In 1883, Cavafy described a condition of symmetric congestive mottling which is probably a universal distribution of a mild form of local asphyxia. In this condition the mottlings or marblings were particularly marked. A similar case was observed in a young man in the Mayo Clinic in the early part of 1920, in whom the mottlings were generally distributed and the skin was cold and clammy. After the most painstaking general physical and neurological examination no organic lesion capable of producing the condition could be demonstrated.

Red. This coloration of the skin is designated by the term "local hyperemia." It was not observed by Raynaud and occurs only infrequently. It may follow either local syncope or asphyxia. It has never been observed alone, unless the simple, burning, tingling, recurrent redness of one or the other external ear so commonly experienced by everyone, and about which there are many superstitions, belongs to this category, and is a common and distinctive demonstration of some vasomotor disturbance which is not associated with any other signs. During the stage of local hyperemia the part is bright red, usually with palpably increased arterial pulsations, increased warmth of the part, slight increase in moisture of the part and at times an unpleasant sensation, almost approaching pain, which is, however, usually described as tingling.

Black. The presence of a blackish discoloration of parts of the body has been designated by various titles such as spontaneous gangrene, idiopathic gangrene and symmetric gangrene, and it is

to this phase of the events described by Raynaud that most importance has been attached. The words symmetric and gangrene have received undue emphasis. In the type of cases originally described by Raynaud if gangrene is lacking or if it is present but does not happen to be symmetric, the case is usually spoken of as "not typical," "not Raynaud's disease," and a diagnosis is not made. The history of the case is classified under some hit-or-miss term, so that it eventually becomes lost for all purposes of study. The gangrene usually affects the peripheral parts, and is of a dry type, with clear demarcation from the normal tissues. The part may continue in a black, dry state for months before finally sloughing. In the language of Raynaud, there is a tendency for the gangrene to be symmetric. It may come on spontaneously, either without syncope or asphyxia, or follow one or both. The parts affected by gangrene heal with a peculiar tapering deformity which is quite striking. The gangrene may appear as a slight ulceration, which heals with a small white scar, or the part may become dry, with thickening of the skin, which is characterized by a brown, scaly desquamation. The gangrene may be massive and involve a finger, a forearm, a leg or even a leg with a portion of the thigh.

Changes in Sensation. Raynaud stated that pain is almost a constant finding; it may be sharp and paroxysmal, coinciding with manifestations of syncopal and cyanotic attacks, or a painful numbness followed by a sensation of burning and shooting. It is not limited to the affected extremities but radiates to every limb. The pain is increased by pressure; it is usually the first symptom to attract attention. Osler observed that pain commenced with the onset of local asphyxia, and he also observed considerable pain in cases in which the stage of gangrene had been reached. The pain may be present in one attack and absent in another. Cassirer observed pain, usually burning, in most cases. He called attention to the lack of either peripheral or spinal distribution.

Analgesia occurs rarely, but infrequently there is a slight diminution of tactile sensation. Heat and cold sensations are not changed. There may be no unusual sensations on returning to normal color after an attack of syncope or asphyxia, or there may be burning, tingling, pricking or a combination of peculiar sensations.

The severity of the pain is illustrated in one of the patients in the Mayo Clinic series who for thirty years had been troubled with attacks of syncope and asphyxia and intense pain in both feet. Cold weather increased the symptoms, but they were present to some extent in all seasons. Treatment did not avail, and each succeeding year the pain became more intense until the patient finally died from what, for want of a better term, was designated "physical exhaustion."

Changes in the Motor System. Motor disturbances such as clumsiness and slowness in performing the ordinary work are commonly present. Barlow has noticed that patients complain chiefly of difficulty in accomplishing small movements.

Changes in the Bones. Cassirer was the first to observe changes in the bones in association with the phenomena of Raynaud. He described the changes as atrophic, a thinning

FIG. 1 (Case 231824).—Thinning of the bony cortex, widening of the marrow space and sharpening of the canalicular systems.

of the cortex of the bone with consequent increase of the marrow space and sharpening of the outline of the canalicular systems. The bone may be completely absorbed without becoming necrotic or forming a sinus. Oppenheim has made similar observations. An atrophic process in both bones of the right leg was observed in a patient in the Mayo Clinic (Case 231824). The changes are clearly shown in Figure 1.

The histories of 67 patients observed in the Mayo Clinic were studied; 50 of these were traced.

TABLE I.—INCIDENCE OF RAYNAUD'S DISEASE IN RELATION TO THE TOTAL REGISTRATIONS OF PATIENTS IN THE MAYO CLINIC EACH YEAR.

Year.	Patients.	Percentage of registrations.
1911	4	0.026
1912	2	0.013
1913	3	0.012
1914	5	0.016
1915	5	0.014
1916	10	0.023
1917	7	0.014
1918	13	0.026
1919	9	0.014
1920	9	0.015

The patients came from twenty-two of the states in the United States and from three provinces in Canada. With the exception of 1 born in Austria, 1 in Italy, 1 in Switzerland and 1 in Holland, all were born in North America. The birthplace, and places of residence are so diversified that they can have no weight as etiological factors.

TABLE II.—40 (59.8 PER CENT) FEMALES AND 27 (40.2 PER CENT) MALES.

Age.	Patients.
Under 10	1
11 to 20	6
21 to 30	20
31 to 40	16
41 to 50	15
51 to 60	7
61 to 70	1
71 to 80	1

Twenty-one definite occupations were represented other than that of housewife. It was not demonstrated that physical and nervous strain incident to any one type of occupation or social stratum was a cause of the condition.

TABLE III.—STATE OF HEALTH (NOVEMBER 15, 1920) OF THE 50 PATIENTS TRACED.

	Patients.
Improved	12
General health good	13
Entirely well	2
No change	9
Worse	8
Died:	
Tuberculosis	1
"Exhaustion" incident to intense pain	1
Influenza	3

The results shown in Table III do not give the usually gloomy outlook for such patients.

TABLE IV.—DURATION OF DISEASE.

	Patients.
5 years or less	37
10 years or less	15
15 years or less	5
20 years or less	4
25 years or less	3
30 years or less	1
35 years or less	0
40 years or less	1
45 years or less	1

It may be definitely stated that a patient may have Raynaud's disease for many years, with more or less good general health. This was illustrated in a patient, aged forty-eight years (Case 305726), who visited the Mayo Clinic in 1920 on account of painful ulcerated areas in her feet. When she was five years of age she began to be troubled with purple spots on her legs which appeared at varying intervals. This kept up until she was twenty-six years of age, when small ulcers appeared on both legs following an attack of blue spots. These ulcers lasted a short time, healed and again appeared. The patient was always well during her pregnancies, and for one period of three years had no trouble. This period represents what may happen when it is believed the condition is cured by some line of treatment. Following this interval blue spots, and at times extreme pallor of the right leg, appeared. In a short time the trouble appeared in the left leg and then in both forearms. There was frequent desquamation of the epidermis of the legs. Shortly before she came to the Clinic, her left great toe became black and intensely painful. Still more recently small ulcers appeared on the left small toes, then on the left third toe and finally on the left great toe. This all took place during the course of three weeks. There had been an ulcer on the right leg more or less constantly for seven years. The patient's general health had been good.

Mode of Onset. Sixty (89.5 per cent) of the patients described the mode of onset as very sudden. Two patients did not describe it and 5 described it as very gradual. "Sudden onset" means that at some particular hour when the patient was in good health a portion of the body suddenly turned white, blue or black. "Gradual onset" means that tingling, numbness, clumsiness or an indescribable discomfort was experienced in attacks, followed at a later period by the color phenomena. In 1 instance the condition followed immediately an attack of diphtheria, in 1 an attack of unexplained jaundice and in 1 it became aggravated after an attack of influenza. This patient was having some vascular disturbance in the fingers. In the other cases it was impossible to find a condition which might be regarded as a causal factor. There was nothing in the histories of

the patients to indicate that the disturbances depended on a toxic process.

TABLE V.—PATIENTS WITH COLOR CHANGES.

	Patients.
Syncope alone	9
Asphyxia alone	6
Gangrene alone	1
Syncope and asphyxia	28
Syncope without gangrene	0
Asphyxia and gangrene	13
Syncope, asphyxia and gangrene	11

The syncopal and asphyxial attacks lasted, as a rule, for from fifteen minutes to one hour. The asphyxial attacks, in 1 case, were continuous for four months before the onset of gangrene. The gangrene lasted usually about two months before sloughing of the part occurred. Local hyperemia with the other vasomotor phenomena of Raynaud's disease was found in 8 (11.94 per cent) patients in this study. The occurrence of this discoloration was clearly shown in a woman, aged forty-one years (Case 331049), who visited the Clinic in 1920 after having suffered for three years with attacks in which the fingers to the metacarpophalangeal joints of both hands, when exposed to cold, became dead white, then purple and in a short time red, then gradually regained their normal color.

TABLE VI.—SENSORY NERVOUS SYSTEM SYMPTOMS.

	Patients.
Intense pain	17
Slight pain	9
Numbness	20
Tingling	11
Pricking	1
Itching	1
Burning	9
Soreness	4

One patient had lost tactile sensation over the dorsal and palmar surfaces of the hands and another patient had anesthesia of both little fingers.

Patients who were troubled with syncopal and asphyxial attacks of the fingers usually experienced clumsiness during the period of the attacks. One patient limped intermittently while he was having syncopal attacks in his legs, which were affected alternately. A similar case was described by Westphal. Motor disturbances were not a common finding.

The lesions were bilateral and symmetric in 38 (56.7 per cent) patients and asymmetric in 29 (43.2 per cent). The tendency to symmetry and the slowly healing gangrenous process are shown in a girl, aged five years (Case 282988), who was brought to the Clinic in 1919 on account of deformities of the lips following a gangrenous process. When she was fifteen months old, purple-red spots appeared

suddenly over the entire body, in the course of which the first two phalanges of the first and second fingers of the right hand turned red, then black, and finally sloughed off. The trouble occurred

FIG. 2 (Case 282988).—Peripheral and symmetric tendency of the lesions with the terminal sloughing in the right forearm. The left forearm shows the atrophic type of gangrene and the gradual sloughing process. The lip margins are in an advanced state of gangrene. The state of nutrition is fairly good, as shown by the fulness of the cheeks. (Courtesy of Dr. Gordon B. New.)

FIG. 3 (Case 282988).—Later stage of patient shown in Fig. 2. Type of scar, deformities and the excellent state of nutrition in the presence of serious feeding difficulties.

during the winter months. One year later she had another attack with small sloughs over the legs; these healed with whitish scar formation. The lower third of both forearms turned black, became gangrenous and then sloughed, and healed with the type of deformity shown in Figures 2 and 3. During this attack the lip margins sloughed off. The child suffered intensely from pain during the process. Since November 15, 1920, she has had syncopal attacks of various parts of the body. This case is similar to a case reported by Raynaud. The patient, a woman, aged twenty years, presented herself at the Academy of Sciences, Paris, bringing her forearms in her coat pockets. They were black and dry like the hands of a little mummy. When she was seven years of age, following a slight fever, a withering process developed in both forearms, which finally sloughed, leaving the two stumps, which she used to draw the unusual relics from her pockets.

TABLE VII.—DISTRIBUTION OF SPONTANEOUS AMPUTATIONS THE RESULT OF GANGRENE.

	Patients.
Little toes	5
Fingers	6
Great toe	2
Both forearms and lips	1
Right femur	1

TABLE VIII.—DISTRIBUTION OF SMALL GANGRENOUS AREAS.

	Patients.
Entire body	19
Fingers	5
Left side of face	1
All of face	2
Knee	1
Side of tongue	1
Back of throat	1

The universal distribution of the scar formation following gangrenous processes is shown in Figures 4 and 5, photographs of a man, aged eighteen years, (Case 144087), who visited the Clinic in 1915 on account of multiple gangrenous areas over the extremities and the trunk. One year before, he had had a sudden attack of cyanosis of the forefinger of the right hand, which continued for four months; the finger then turned black and gangrenous. The tip of the finger finally sloughed and the process spread up the finger. Early in the condition the right ring finger and little finger became cyanotic. Three weeks after the primary onset the third, fourth and fifth fingers of the left hand became cyanotic, and this continued off and on for eight months, when gangrene developed in the left hand. Later his knees, the side of his tongue and many small areas over the body became cyanotic. These areas finally became gangrenous, sloughed and healed, with small white scar formation. At the time

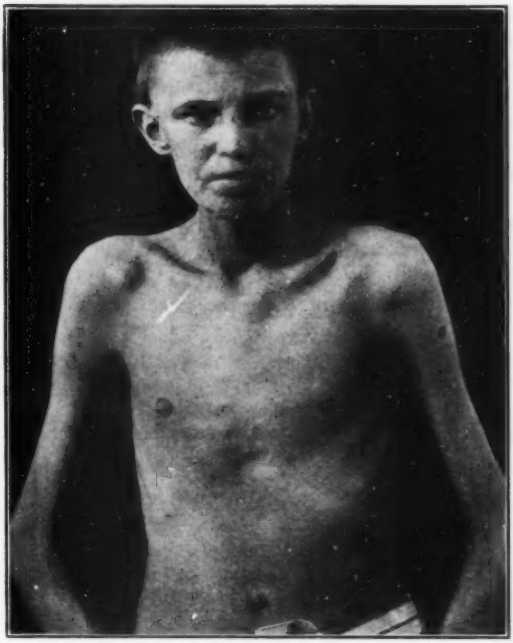

FIG. 4 (Case 144087).—Minute scars which represent the results of previous gangrenous areas. The patient was markedly emaciated.

FIG. 5 (Case 144087).—Tendency to symmetric distribution of the gangrene. Multiple scar formation on the forearms.

of his visit to the Clinic the condition was widespread, and he was in a state of marked physical exhaustion. The pain was increasingly severe with each new attack. November 15, 1920, he was still alive but little improved, except for the disappearance of the pain. The syncopal attacks in the fingers had not been marked, and they continue. They are usually followed by asphyxial attacks.

Blood-pressure. The systolic blood-pressure was within normal limits in 49 (73.1 per cent) patients, above normal in 11 (16.4 per cent) and below normal in 7 (10.4 per cent). The diastolic blood-pressure was within normal limits in 14 (20.8 per cent) patients, above normal in 33 (49.2 per cent) and below normal in 12 (17.8 per cent).

TABLE IX.—EVIDENCE OF NO RELATIONSHIP BETWEEN PHENOMENA OF RAYNAUD AND PULSE-PRESSURE.

Pulse-pressure, mm. Hg.	Patients.
10 to 20	1
21 to 30	5
31 to 40	24
41 to 50	16
51 to 60	6
61 to 70	4
71 to 80	1
91 to 100	1
100 to 110	1
Not recorded	8

The absence of a fixity of blood-pressure variations in a vasomotor disturbance coincides with the experimental work of Krogh.

Blood Picture. The hemoglobin was recorded in 45 (61.1 per cent) patients. The percentage ranged from 47 to 88, with an average of 81. The erythrocytes were counted in 34 patients, and ranged from 2,820,000 to 5,890,000 per cmm., with an average of 4,810,000 per cmm. The leukocytes were counted in 34 (50.7 per cent) patients, and the lowest count was 5600 cells per cmm.; the highest was 13,400 cells per cmm., with an average of 7800 cells per cmm. A differential count was made in 12 patients. The average type of cell found was: polymorphonuclears, 63.1 per cent; eosinophils, 4.5 per cent; small lymphocytes, 23.9 per cent; large lymphocytes, 4.5 per cent; and basophils, 1.4 per cent. One patient had a marked secondary anemia.

Pulse-rate. The pulse-rate was normal in 12 patients, increased in frequency in 4 and lessened in frequency in 26; it was not recorded in 25.

Urine. The examination of the urine was negative in all cases. Hemoglobinuria was not observed in any case.

TABLE X.—RELATION OF SEASON AND EMOTION TO ATTACKS.

	Patients.
Cold	51
Cold and emotion throughout the year	2
Emotion	5
Cold of winter months	7
Cold of autumn months	1
No apparent exciting factor but attacks throughout year	20
No apparent exciting factor; attacks limited to summer months	1

To the patients who had symptoms throughout the year, the search for fixed temperatures became an obsession. One of the patients was financially able to afford to change her location every few months; in this manner she had passed through several years without trouble. She was subject to local syncope and asphyxia, the most troublesome type from the standpoint of actual suffering.

Incidental Findings. One patient was always well during her pregnancies. Menstruation was suppressed in 1 patient during the period of attacks; 1 had excessive menstruation; 1 had irregular menstruation; and 1 had transient attacks of hemiplegia during the attacks. One man was sexually impotent during the attacks. The patients observed that if they pricked their fingers during the stage of local syncope no bleeding occurred. One patient had eighteen convulsions during the two years that she had been suffering from Raynaud's phenomena. This patient was also subject to migraine, so that it is debatable whether her convulsions were owing to vasomotor changes of the new condition or whether they were the expression of the migraine-epilepsy syndrome.

Associated Conditions. One patient had asthma; 1 had duodenal ulcer; 3 patients had migraine; 1 patient had angioneurotic edema; 1 patient had pulmonary tuberculosis; and 1 patient had hysteria. Pathological changes extensive enough to justify the belief that they had any relation to the vasomotor phenomena were not observed. All the patients had negative Wassermann reactions on the blood and histories negative for syphilis.

Measures for Relief. The attacks were relieved by warmth in 5 patients; by cold applications in 1 patient; and 1 patient was relieved by taking Blaud's pills. Bier's hyperemia was tried in all the early cases, but no benefit was obtained. No patient was relieved by elevation of the affected part. A warm, non-variable climate seemed to be the only factor to afford relief. Some of the patients were able to lessen their attacks by wearing woolens and protecting themselves from the cold as much as possible. Thyroid extract produced no definite benefit. The eradication of foci of infection was without results.

Discussion. The basic mechanism involved in the production of the symptoms manifested in Raynaud's disease remains obscure, but the phenomena observed coincide satisfactorily with the theoretic and experimental possibilities of a disturbance of the vasomotor appar-

atus. The attacks of syncope are no doubt constrictor, as the part or parts are partially or completely bloodless during the attacks. This is shown by the absence of hemorrhage on pin prick, and further by the total lack of color of the part and the lowered temperature. The asphyxial attacks are probably also constrictor and not dilator, as is commonly believed. The cyanosis may be the result of a slowing of the passage of blood through the peripheral vasculature with its consequent prolonged retention in the parts; this is due to the increased resistance with which it meets on account of the partially or in places completely constricted lumina of the finer bloodvessels. That the local asphyxia is constrictor, but to a less extent than that observed in syncope, is further substantiated by the lessened degree of lowered temperature. Any explanation which fails to consider the constriction as involving arterioles, capillaries and venules is unsatisfactory. A limited constriction of the arterioles and capillaries would result in a swelling of the tissues above the site of constriction and a cyanosis beyond the point of constriction. This is not observed in the phenomena of Raynaud. A constriction of the venules would result in a swelling in the regions to the proximal side of the constriction. This is not observed. The condition must involve all three of the finer ramifications of the vascular system in order to produce the ordinary consequences of the condition. The hyperemia is dilator, as evidenced by the color, the increase of temperature of the part and the palpable pulsations of the finer peripheral vessels.

The search for a tangible causative factor has been without results. It is not possible to attribute the condition to toxemia, as no possible toxic cause is visible. The infrequency of acute infections in the onset minimizes the importance of the ordinary type of infections as etiological factors. Heredity plays no part. Whatever may be the causal agent the method of its action seems in most cases peripheral on the vasomotor nerves rather than on the central mechanism, although it is possible that in certain cases both may be affected.

The name for the disease has always been indefinite. For a better understanding of the particular phase of the disease discussed the term "Raynaud's disease" should be discarded and in its place "local syncope of Raynaud," or "local asphyxia of Raynaud," or "gangrene of Raynaud" substituted. Various combinations of these terms can be used so that the phase of the condition under discussion may be easily understood. When all three phases of the condition are present the term "phenomena of Raynaud" would be a satisfactory substitute.

BIBLIOGRAPHY.

1. Barlow, T.: Raynaud's disease, in System of Medicine, Allbutt, C., and Rolleston, H. D. London, Macmillan & Co., 1910, **7**, 120–149.

2. Bernard, C.: Experience sur les functions de la portion céphalique du grand sympathique. Compt. rend. soc. de biol., 1852, **4**, 155.
3. Boyer, A.: Quoted by Raynaud.
4. Brown, W. L.: The Sympathetic Nervous System in Disease. London, H. Frowde, 1920, 114–116.
5. Brown-Séquard, C. E.: Sur les resultats de la section et de la galvanisation du nerf grand sympathetique au cou. Paris, E. Thunot, 1854, 9 pp.
6. Cassirer, R.: Die vasomotorisch tropischen Neurosen. Berlin, S. Karger, 1901, 609 pp.
7. Cassirer, R.: Handbuch der Neurologie. Berlin, Springer, 1914, **4**, 185, 203.
8. Cavafy, J.: Symmetrical Congestive Mottling of the Skin. Trans. Clin. Soc. London, 1883, **16**, 43–48.
9. Gruber, C. M.: The Response of the Vasomotor Mechanism to Different Rates of Stimuli. Am. Jour. Physiol., 1917, **42**, 214–227.
10. Gunning, R. E. L.: Comparative Vasomotor Reactions in Branches of the Arterial Tree. Am. Jour. Physiol., 1916, **41**, 1–4.
11. Heger: Quoted by L. Luciani, Human Physiology. London, Macmillan & Co., 1911, **1**, p. 355.
12. Krogh: Quoted by Policard.
13. Martin, E. G., and Mendenhall, W. L.: The Response of the Vasodilator Mechanism to Weak, Intermediate, and Strong Sensory Stimulation. Am. Jour. Physiol., 1915, **38**, 98–107.
14. Oppenheim, H.: Lehrbuch der Nervenkrankheiten. Berlin, S. Karger, 1913, 1941 pp.
15. Osler, W.: Vasomotor and Trophic Disorders, in Modern Medicine, Osler and McCrae. Philadelphia, Lea & Febiger, 1915, **4**, 975–997.
16. Pilcher, J. D., and Sollman, T.: Studies on the Vasomotor Center. Jour. Pharmacol. and Exper. Therap., 1914–1915, **4**, 323–411.
17. Policard, A.: Les phénomènes de motricité capillaire. Lyon chir., 1921, **18**, 51–68.
18. Porter, W. T.: The Vasotonic and Vasoreflex Center. Am. Jour. Physiol., 1915, **36**, 418–422.
19. Raynaud, M.: De l'asyphxie locale et de la gangrène symmétrique des extrémités. Paris, Rignoux, 1862, 177 pp.
20. Raynaud, M.: Nouvelles recherches sur la nature et le traitement de l'asphyxie locale des extrémités. Arch. gén. de méd., 1874, **153**, 5–21.
21. Solis-Cohen, S.: Vasomotor Ataxia: A Contribution to the Subject of Idiosyncrasies. Am. Jour. Med. Sc., 1894, **107**, 130–147.
22. Westphal, A.: Ueber hysteriche Pseudotetanie mit eigenartigen vasomotorischen Störungen. Berl. klin. Wchnschr., 1907, **44**, 1567–1570.

THE SPLEEN AND DIGESTION.

Study II. The Spleen and Pancreatic Secretion

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The theory of a functional relationship between the spleen and the pancreas has received much study. Especially in continental Europe in the closing years of the nineteenth century and the first few years of the twentieth century publications of experimental researches in the various languages by numerous investigators were

frequent, and discussions at meetings of physiologists were rife. This turmoil was largely owing to the continual stirring up which the scientific world received at the hands of Herzen, at Lausanne, who, though he found this world largely skeptic of his tenets, nevertheless persisted throughout the major portion of his life in battling persistently for his beliefs.

Review of the Literature. The idea that the spleen in some way influences the pancreas is apparently modern, and does not date as far back in medical antiquity as does the assumption of a similar relationship between the spleen and the stomach. Yet even in the seventeenth century a possible function of the spleen in pancreatic digestion had been suggested. This doctrine was reviewed by Daniel Duncan, of the famous faculty of Montpellier, in 1683: "L'acide fixé du suc pancréatique et le voisinage du pancréas et de la rate, pourroient bien faire croire à quelqu'un que cette glande est l'émonctoire de ce viscère; et que comme le sang de la veine porte va passer par le foye pour quitter les soufres dont il est chargé, ainsi, le sang de la veine splenique se va de charger dans le pancréas de ce suc aigre qu' il a pris dans la rate." Duncan did not subscribe entirely to the view thus expressed. He had never seen the canal between the two organs which some anatomists of his epoch had pretended to have found, and he believed the route from the spleen to the pancreas was more circuitous. He believed the product of the spleen to be poured into the torrent of the general circulation and then brought to the pancreas through a branch of the celiac artery. How similar to the modern conception of internal secretion this is!

The eminent physiologist, Schiff, having been interested by the apparent synchronism between the swelling of the spleen during digestion and the occurrence of trypsin in large quantities in the pancreatic juice or infusions of the pancreas, formulated, in 1862, a definite theory of a splenic-pancreatic relationship. His deductions were drawn from the results of a series of experimental inquiries. The most important of these were (1) experiments in which the tryptic activities of pancreatic infusions from normal animals were compared with those from animals with the spleen removed or functionally cut off by ligature of the splenic pedicle, and (2) experiments in which the amounts of digested albumin introduced into the duodenum (either with the duodenum ligated at both ends or in duodenal fistulas) were tested in normal and splenectomized dogs. His results led him to believe that after extirpation of the spleen, anatomically or functionally, trypsin fails to appear in the pancreatic juice or in an infusion of the gland during that stage of digestion in which it is normally present. He concluded that "die eiweissverdauende Kraft des Pankreas in jeder Verdauungsperiode durch die Milz und ihre Volumenzunahme bedingt wird." He then put forward the hypothesis, conforming to his

famous "peptogen" theory, that during congestion a substance is produced within the spleen which is carried away by the blood and gives to the pancreas the wherewithal to form its peptonizing ferment.

Lussana (1868), Schindeler (1870), Ewald (1878), Bufalini (1879) and Malassez (1881), by various methods of experimentation, were unable to demonstrate any impairment of the tryptic activity of pancreatic juice or infusions after splenectomy. Thus Schiff's research seemed discredited and his theory disproved.

The final acceptance of the part of the zymogens, discovered by Heidenhain and announced in 1872, threw all evidence thus far submitted out of court and necessitated a complete reopening of the subject. Herzen, who had formerly been Schiff's laboratory assistant at Florence and had confirmed his chief's results, tried to unravel the tangle caused by modifying Schiff's hypothesis. He argued thus (I am quoting, with slight modifications, his pupil Bellamy): Since the zymogen even in splenectomized animals is being continuously elaborated, and therefore independent of the spleen and its periodic congestion; and since zymogen accumulates in the gland cells during fast, but becomes rapidly and copiously transformed into trypsin only in the presence of the spleen and in direct proportion to the splenic dilatation, it seems feasible that the spleen produces by "internal secretion" during its congestion an unknown substance which, carried away by the circulating blood, transforms the inert zymogen, already deposited in the pancreas, into active trypsin. Herzen performed many experiments to demonstrate this. These experiments, *in vitro*, were tests of tryptic digestion in which he employed aqueous boric acid and glycerin infusions of the pancreas and spleen.

The digestive tests of Herzen were repeated by Carvallo and Pachon (1893), but with negative results. However, after communicating with Herzen, Pachon conscientiously went over his experiments and, with his collaborator, Gachet, was converted entirely to Herzen's point of view. Gachet and Pachon devised an intravenous injection experiment which became much used. By it they ascertained that good tryptic digestion by pancreatic infusions obtained from splenectomized animals could be secured only after the intravenous injection of an infusion of congested spleen.

Much less striking were the results of Badano (1900), who used both the infusion method of Herzen and the injection method of Pachon: yet his findings were confirmatory of those of these workers.

The crowning and ultimate effort made by the Herzen school is represented in the work and writings of Besbokaia and Bellamy. The latter considers the splenic internal secretion to be carried to the pancreas by the solid elements of the blood, and insists, as did

Herzen, "The pancreas of a dog deprived of its spleen exists in a condition of complete and permanent atrypsia."

Much in line with this so-called "freighting" theory of a pancreatic activating splenic hormone are the findings of Mendel and Rettger at Yale (1902-1903). From their work they concluded: "(1) Extracts of the spleen, prepared from the organ when congested during digestion, increase the proteolytic power of the pancreas. This was demonstrated *in vitro* and *in vivo*. (2) Injections of defibrinated blood from the splenic vein are likewise effective. (3) A boiled extract of spleen is ineffective. (4) Extracts of other tissues (liver, pancreas) apparently have little action. The same is true of pure saline infusions. (5) The precipitate produced by the addition of alcohol to active splenic extracts contains a trypsinogenic substance. (6) The extracts of the pancreas of splenectomized dogs are not always free from trypsin. Whether this is entirely attributable to an extrapancreatic transformation of trypsinogen is not determined."

A permanent pancreatic fistula, made by the technic of Pawlow, was first made use of in the study of this problem by Popielski (1901). He could find no activation of trypsinogen by any splenic ferment. Pawlow, under whom Popielski worked, states from his own observations that he considers Herzen to have greatly overrated the part of the spleen in pancreatic digestion and that Herzen's assumptions do not correspond with the facts.

A critical survey of the errors of previous investigators has been made by Silvestri (1901). As the result of a diligent series of researches he could not subscribe to the ideas of Herzen and Gachet and Pachon. He considered that the spleen favored the proteolytic power of pancreatic extracts by means of the kinase furnished by the leukocytes so abundant in this organ.

A novel and ingenious experiment was performed by Frouin in 1902. He isolated the stomach from the alimentary tract in dogs and then performed splenectomy. The removal of the spleen did not apparently interfere with the nutrition of the animals even when on a meat diet. He argued that since the nutritive condition of splenectomized animals remained excellent when gastric digestion was excluded, it was improbable that there had been any deficiency in the secretion of tryptic pancreatic ferment.

A histologic investigation of the effect of ablation of the spleen on the formation of zymogen granules in the alveolar cells of the pancreas was made by Tiberti in 1903. He could demonstrate no change following splenectomy.

In the endeavor definitely to settle the subject of a splenic-pancreatic relationship, Prym, in 1904 and 1905, carried on a most exhaustive series of researches. He used permanent pancreatic fistulas in the first investigation. From data thus obtained his most important conclusions were: The normal dog with a per-

manent pancreatic fistula, made according to the method of Pawlow, secretes after each feeding for each digestive period a pancreatic juice which contains only protrypsin if the juice is prevented from coming in contact with the intestinal mucosa by probing the duct; contact with the intestinal mucosa for a short time, or even the addition of small amounts of fresh intestinal juice, changes protrypsin into trypsin; the amount of proteolytic power of the pancreatic juice is not influenced in any recognizable way by splenectomy; intravenous injections of splenic infusions by the method of Gachet and Pachon have no influence on pancreatic secretion in the splenectomized dog with a permanent pancreatic fistula. In a second investigation Prym made use of pancreatic and splenic infusions as employed by Herzen. He found (as was also shown by Hekma) that when boric acid is used in the preparation of pancreatic infusions, bacteria play an important part in changing protrypsin into trypsin. When in like manner glycerin is used as a vehicle, the water content of the infusion is a matter of prime importance. In conclusion, he asserts that the spleen has no part in the activation of trypsinogen.

Further observations on two dogs with permanent pancreatic fistulas (Pawlow technic) were made by Lombroso and Manetta in 1915. From their results they were led to believe that the three enzymes of the pancreatic juice (trypsin, lipase and amylase) do not vary in any way after splenectomy, but that the amount of pancreatic secretion increases to a remarkable degree.

In the course of studies conducted on the general subject of the part played by the spleen in digestion, I have taken up again the question of a splenic-pancreatic relationship. This has been prompted by the conflicting results of the investigations just reviewed, by the allusions met with in scientific literature wherein the status of the Schiff-Herzen hypothesis is still assumed to be unsettled, and by the opportunity afforded by the perfection of a technic for the formation of a permanent pancreatic fistula which permits reducing sources of error to a minimum.

Experimental Methods. Observations were made on dogs with permanent pancreatic fistulas. The technic employed in making these fistulas has been given in detail in a previous communication.[40] Briefly, the salient features of the operative procedure are transplanting the duodenum under the skin of the abdomen with twisting of the duodenal axis to the right; severing the major pancreatic duct at its entrance into the gut; and bringing the duct to the surface through a stab wound in the skin away from the primary operative incision. This method gives fistulas which secrete a juice with inactive proteolytic ferment. Such a juice is much to be desired, since it permits of accurate activation of the trypsinogen after collection, and does not digest and erode the abdominal wall of the animal.

The pancreatic juice was collected by strapping the animals to a frame and applying a metal funnel over the duct opening. Three hundred grams of raw meat cut into small cubes were given as a secretory meal. At other times the diet consisted of dog biscuit and milk, and small amounts of soda bicarbonate were fed in order to make up for the alkali lost in the juice secreted from the fistula. The dogs were deprived of food for about eight hours and of water for two hours previous to beginning each experiment. Collections of juice were made for four or more hours after giving a secretory meal.

The amount of juice secreted hourly was measured and its proteolytic activity determined in all instances. Special experiments were conducted in which lipolytic and amylolytic fermentative power and the degree of alkalinity of the juice were ascertained.

The trypsinogen of the juice was activated into trypsin by the addition of an enterokinase solution prepared after the method of Bayliss and Starling; that is, by digesting the scrapings of mucosa of dog's duodenum in chloroform water for two days, then filtering, first through ordinary filter paper, and second through a Berkefeld filter. Mett's tubes, coagulated at 85°, were used to determine the tryptic digestive activity; 5 cc of pancreatic juice, 1 cc of enterokinase solution and two sections of Mett's tubes were placed in the thermostat at 39° for twenty-four hours. The results obtained were expressed directly in the number of millimeters of albumin digested (average of four readings).

The lipolytic activity was tested by adding 2 cc of pancreatic juice to 1 cc of neutral olive oil. The mixture was well shaken and placed in the thermostat at 39° for twelve hours. Then 5 cc of 95 per cent alcohol were added and the amount of fatty acids determined by titration with tenth normal sodium hydroxide, using phenolphthalein as an indicator. In the tables the lypolytic activity has been expressed directly as the number of cubic centimeters of tenth normal sodium hydroxide required to affect neutralization under these conditions.

Amylolytic activity was measured by a slightly modified Robert's method. The starch paste solution was boiled for five minutes. The iodin solution used was prepared by diluting 1 cc of a solution of: potassium iodid, 4 gm.; iodin, 2 gm.; water, 250 cc to 100 cc. One cubic centimeter of juice was placed with 100 cc of 0.1 per cent starch paste at 40° for three minutes; then 1 cc of the iodin solution was added to 1 cc of the mixture and the time noted when the achromic point was reached. After the achromic point had been obtained within four to six minutes after the addition of the enzyme the amylolytic activity was calculated by the formula $D = \frac{10}{V} \times \frac{5}{N}$, when V = volume of enzyme solution and N = time in minutes required to reach the achromic point. D is the number

of cubic centimeters of 1 per cent starch paste hydrolyzed to the end point in five minutes by 1 cc of juice.

Besides the unit concentrations of trypsin, lipase and amylase, comparative figures are tabulated representing the average total digestive unit of each enzyme secreted for each hour. These figures have been reached for trypsin and steapsin (since these ferments when determined quantitatively by these experiments obey the law of Schütz and Borissow for enzymic activity) by multiplying in each instance the square of the enzyme value or concentration for each hour by the amount of juice secreted that same hour; these results have been added, the sum divided by the number of days on which observations were made, and thus an average comparative amount for the total output of enzyme for each hour obtained. In the case of amylase a similar procedure was employed, save that the enzyme value on concentration was not squared, since in this instance the Schütz-Borissow law does not apply, but the amount of digestion varies directly with the concentration of the enzyme.

For the determination of the degree of alkalinity, 5 cc of pancreatic juice was incinerated, dissolved in 25 cc of distilled water and titrated with tenth normal hydrochloric acid, using phenolphthalein as an indicator. In the tabulation the alkalinity has been expressed by the number of cubic centimeters of tenth normal hydrochloric acid required to effect neutralization under these conditions.

After establishing a norm for the amount of pancreatic secretion and its ferment content, splenectomy was performed on three dogs, one of which died after the operation. Observations are also given on one animal which was not splenectomized. All operative procedures were conducted under ether anesthesia with the employment of sterile technic.

Protocols. D 697: A male mongrel in good condition, weighing 14 kg. A two-stage operation for pancreatic fistula was performed; the duodenum was transplanted under the skin May 27, 1920, and the fistula established July 21. The animal continued in good health and maintained its weight. Between September 6 and 20, however, during which time no observations were made and no prophylactic dilation of the fistular orifice performed, the pancreatic duct strictured and closed. September 22, the dog was etherized and an attempt made to reëstablish the patency of the duct, but this proved unsuccessful and further continuance of the experiment was impossible (Table I).

D 701: A female mongrel in good condition, weighing 21.3 kg. May 28, 1920, a one-stage operation for pancreatic fistula was performed. The major pancreatic duct was quite small and divided into six branches close to its duodenal attachment. Pancreatic secretion from the fistula began four days later and con-

tinued normally until June 17, when a stricture occurred about 0.6 cm. from the orifice. A few days later the stricture was passed with a sound and a dilatation of the duct found behind it. From this time on the duct remained patent. There was a slight loss of weight. (Table II).

Splenectomy was performed July 7. Twelve hours later the animal died. At necropsy cause for death could not be found. The terminal portion of the pancreatic duct was dilated to twice normal size. The pancreas was normal. There were a few hemorrhagic areas in the omentum just proximal to the point of ligation of the splenic vessels. The common bile duct was dilated to four times normal size. There was a slight hypostatic congestion of the lungs.

D 719: A male mongrel collie in good condition, weighing 13.7 kg. June 5, 1920, a one-stage operation for pancreatic fistula was performed which was exceptionally successful. July 23, splenectomy was performed. The animal remained in excellent condition, although it had lost 2 kg. in weight at the end of two and one-half months. September 12, about three weeks after the close of the experiment, a continuous secretion of pancreatic juice appeared. Anorexia became marked and the animal lost weight rapidly and died September 22, three months and eighteen days after the establishment of the fistula. (Table III.)

At necropsy the pancreatic duct was found to be patent. The pancreas appeared to be normal. There was no accessory splenic tissue. A hair ball 5 cm. in diameter was found in the stomach.

E 130: A female mongrel in good condition, weighing 10.2 kg. December 7, 1920, a one-stage operation for pancreatic fistula was performed. The fistula was eminently successful and the animal gained weight slightly. January 4, 1920, splenectomy was performed. Two weeks after the close of the experiment the duct strictured about 2 cm. from the surface; however, the patency of the duct reëstablished itself without interference and pancreatic secretion from the fistula continued until the date of death. The animal gradually lost weight, and March 10, 1921, was killed by bleeding under ether on account of the marked inanition which had developed. The fistula had functionated three months and three days. (Table IV.)

At necropsy the pancreatic duct was found to be patent and the abdominal wall wet with pancreatic fluid. The pancreas was normal. Destruction of acinar tissue or pancreatic infection was not revealed by microscopic examination. There was no accessory splenic tissue.

Review of Experimental Data. The tables of experimental data show that in this set of experiments splenectomy caused no changes in pancreatic secretion which were definite and constant enough to justify the postulation of a functional splenic-pancreatic relationship.

In every instance the pancreatic juice collected did not contain active trypsin.

TABLE I.—DETERMINATIONS OF NORMAL PANCREATIC SECRETION OF DOG D 697—SECRETORY MEAL, 300 GM. OF MEAT.

1920.	Amount of secretion.							Trypsin (Mett's tubes).						
	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.	Fifth hour, cc.	Sixth hour, cc.	Seventh hour, cc.	First hour, mm.	Second hour, mm.	Third hour, mm.	Fourth hour, mm.	Fifth hour, mm.	Sixth hour, mm.	Seventh hour, mm.
Aug. 11	13.7	9.3	9.0	9.3	..	..	..	3.60	4.00	4.40	3.95			
Aug. 20	23.5	15.2	17.1	13.0	15.0	13.8	7.2	2.40	2.95	3.20	3.90	4.20	4.0	3.7
Aug. 23	7.0	5.0	10.8	11.5	6.4									
Aug. 26	8.1	10.0	7.0											
Aug. 28	10.5	24.0	37.5	44.8	29.4	18.4	16.0							
Sept. 1	13.8	22.5	25.9	27.3	16.0	..	..	5.30	5.00	5.10	4.60	5.10		
Average	12.8	14.3	17.9	21.2	26.7	16.1	11.6	3.77	3.98	4.23	4.15	4.65	4.0	3.7

TABLE II.—DETERMINATIONS OF NORMAL PANCREATIC SECRETION OF DOG D 701—SECRETORY MEAL, 300 GM. OF MEAT.

1920.	Amount of secretion.							Trypsin (Mett's tubes).						
	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.	Fifth hour, cc.	Sixth hour, cc.	Seventh hour, cc.	First hour, mm.	Second hour, mm.	Third hour, mm.	Fourth hour, mm.	Fifth hour, mm.	Sixth hour, mm.	Seventh hour mm.
June 29	10.4	38.0	24.0	14.4	..	..	..	3.1	2.8	3.50	4.0			
June 30	7.8	11.0	7.6	11.5	18.8	13.2	..	3.5	4.2	4.10	4.4	3.90	4.7	
July 2	51.6	41.3	27.8	12.5	..	..	..	2.5	3.0	3.80	3.6			
July 6	21.0	11.0	30.0	29.2	17.7	20.7	19.8	2.6	2.3	2.40	2.5	2.40	2.5	2.4
Average	22.7	25.3	22.35	17.4	18.25	16.95	19.8	2.9	3.1	3.45	3.6	3.15	3.6	2.4

The results given in Tables I and II have been included to illustrate further the normal findings of pancreatic secretion under the conditions of this study and to serve as controls for the results in the splenectomized animals presented in Tables III and IV. In most instances the amount of pancreatic juice secreted was greatest within the first two hours after the secretory meal and rapidly decreased thereafter, so that the major portion of the secretion for each digestive period occurred within the first four hours. This agrees with the curve of pancreatic secretion on a meat diet given by Pawlow. The tryptic activity ordinarily was sufficient to digest from 3 to 4 mm. of albumin (Mett's tubes) in twenty-four hours; it fluctuated hourly and reached its height during the third and fourth hours.

TABLE III.—DETERMINATIONS OF PANCREATIC SECRETION BEFORE AND AFTER SPLENECTOMY IN DOG D 719. SECRETORY MEAL, 300 GM. OF MEAT.

1920	Amount of secretion.					Trypsin (Mett's tubes).					Steapsin $\frac{N}{10}$ NaOH for neutralization.					Alkalinity $\frac{N}{10}$ HCl.
	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.	Fifth hour, cc.	First hour, mm.	Second hour, mm.	Third hour, mm.	Fourth hour, mm.	Fifth hour, mm.	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.	Fifth hour, cc.	First hour, cc.
						BEFORE SPLENECTOMY.										
July 8	28.8	42.1	23.8	19.0	19.0	2.09	3.10	3.00	3.00	3.0	0.50	0.70	0.8	1.80	...	3.0
July 12	22.5	16.3	14.3	11.0	...	2.30	2.70	2.90	3.00							
July 14	29.4	18.0	21.3	15.0	9.0	2.85	3.10	3.00	3.10	3.4						
July 16	14.7	4.3	5.6	7.5	6.9	2.00	3.10	3.20	2.90	2.6	0.80	1.30	3.1	2.30	....	2.40
July 19	28.7	98.5	2.7	2.4	...	2.40	2.75	...	...	...	0.70	0.90	0.9	2.00	...	2.97
Average	24.8	19.8	13.5	11.0	11.6	2.49	2.95	3.00	3.00	3.0	0.70	0.97	1.6	2.03		
Average total digestive units	...	...	...	...	...	165	172	146	119	107	10	14	24	37		
						AFTER SPLENECTOMY.										
July 28	33.0	2.22	7.0	9.8	...	2.75	3.25	3.90	2.40	...	0.40	0.90	0.8	0.80		
Aug. 2	14.0	8.50	11.4	9.1	...	1.70	1.90	1.20	2.80	...	0.50	1.00	1.6	2.80		
Aug. 4	29.5	15.4	8.8	4.4	...	1.95	2.35	2.40	2.55	...	...	...	...	...	...	3.10
Aug. 11	14.4	2.9	2.4	1.0	...	3.05	3.20	3.60	3.20	...	...	...	...	...	...	2.40
Aug. 13	18.0	20.0	32.8	8.6	3.5	1.65	1.66	1.55	2.30	...	1.20	0.80	0.7	3.20	4.50	
Aug. 16	32.0	7.7	6.1	2.3	...	2.00	2.70	2.70	...	...	0.70	0.70	0.8	1.20	...	3.70
Aug. 18	25.3	12.5	9.6	4.2	...	2.60	2.35	...	...	...	0.90	0.80	1.2			
Aug. 20	18.3	10.0	...	...	...	...	...	...	...	...	0.40	0.50				
Aug. 23	20.5	11.0	7.3	6.6	...	...	...	...	...	...	...	2.50				
Aug. 26	12.7	6.4	4.0	6.0	...	3.10	3.80	3.70	3.40	...	...	...	8.5			
Aug. 28	26.6	20.6	8.6	7.0	...	...	...	...	...	...	1.90	1.30	0.5	0.70		
Sept. 1	32.7	24.0	9.4	12.0	...	4.10	3.30	4.70	2.80	...						
Average	23.1	13.4	9.8	6.5	3.5	2.54	2.70	2.97	2.78	...	0.67	0.95	2.0	1.74	4.5	3.07
Average total digestive units	...	...	...	...	...	176	66	69	45	...	24	18	51	34		

TABLE IV.—DETERMINATIONS OF PANCREATIC SECRETION BEFORE AND AFTER SPLENECTOMY IN DOG E 130, SECRETORY MEAL, 300 GM. OF MEAT.

Date.	Amount of secretion.				Trypsin (Mett's tubes).				Steapsin $\frac{N}{10}$ NaOH for neutralization.				Amylase (value of D).			
	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.	First hour, mm.	Second hour, mm.	Third hour, mm.	Fourth hour, mm.	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.
							BEFORE SPLENECTOMY.									
Dec. 20, 1920	24.5	11.0	6.5	2.5	3.90	3.60	3.85	3.90								
Dec. 24, 1920	22.3	12.2	7.3	8.3	4.20	4.70	4.90	5.00								
Dec. 27, 1920	18.2	4.5	...	...	2.80	5.40										
Dec. 29, 1920	17.5	12.5	6.3	5.8	...	...	...	...	3.50	6.50	7.00	...	16.0	22.2		
Dec. 31, 1920	25.7	18.4	13.0	6.0	4.45	4.80	5.00	8.20	10.00	8.30	7.00	...	20.9	28.6	30.8	111.1
Jan. 3, 1921	15.3	10.6	7.8	2.5	4.30	4.40	4.45	4.75	7.00	9.50	6.60	...	62.5	55.5	71.3	
Average	20.6	11.5	8.5	5.0	3.93	4.58	4.55	5.46	6.83	8.1	6.86	...	49.7	53.2	51.0	111.0
Average total digestive units	...	...	...	...	339	252	188	176	1200	920	426	...	624	464	478	666
							AFTER SPLENECTOMY.									
Jan. 7, 1921	20.0	11.0	7.5	10.0												
Jan. 10, 1921	22.7	9.2	5.0	8.8	3.50	4.15	4.50	4.50	4.30	3.00	...	1.50	20.0	44.4	...	50.0
Jan. 12, 1921	41.5	40.8	34.2	17.8	3.60	3.55	3.55	4.10	1.10	0.90	0.90	1.10	15.6	12.5	27.7	20.8
Jan. 14, 1921	34.6	27.6	18.4	18.2	3.80	3.80	4.20	4.20	3.00	1.80	2.20	3.80	17.9	13.9	20.8	25.0
Jan. 17, 1921	30.6	24.7	30.0	14.0	3.90	3.80	3.70	3.95	5.50	4.50	4.50	3.00	33.3	27.7	27.7	35.7
Jan. 19, 1921	24.3	12.0	10.0	8.5	4.00	4.40	4.90	4.70	1.40	2.40	1.60	1.00	31.3	27.7	41.7	35.7
Average	28.8	20.9	17.5	12.9	3.76	3.94	4.17	4.29	3.06	2.52	2.30	2.10	23.6	25.2	29.5	70.9
Average total digestive units	...	...	...	...	433	328	301	353	253	155	149	88	704	464	645	414

In Table III it is seen that the amount of secretion, the average concentration of trypsin and of steapsin, and the degree of alkalinity of the pancreatic juice were practically the same before and after splenectomy. However, when the average total digestive units are compared, it will be noted that there was a decrease in the total amount of trypsin secreted in the second, third and fourth hours, whereas the total amount of steapsin secreted was increased save in the fourth hour.

In Table IV it is seen that the amount of secretion after splenectomy was markedly increased, especially during the second, third and fourth hours; the concentration of trypsin was slightly decreased, that of steapsin and that of amylase very much so. However, when the average total digestive units are compared it is noted that the total amount of trypsin secreted was really increased, and the amount of amylase practically the same as before removal of the spleen, although the amount of steapsin was reduced.

Hence, when the many uncontrollable factors that must enter into experiments of this type are taken into consideration, it is realized that the minor changes that occurred after splenectomy might be expected. The increase in the amount of secretion (Table IV) may possibly be explained as resulting from disturbances in the splanchnic circulation due to the severance and ligation of the splenic artery and vein.

The changes in the secretion of trypsin are negligible and the data given seem to justify definite assertion that splenectomy exerts no influence on the trypsinogenic function of the pancreas. The amount of amylase secreted was the same after removal of the spleen as before. The amount of steapsin in one instance was slightly increased, in the other much decreased, thus on the whole showing no definite change; however, the same weight cannot be attached to the figures for steapsin as that given to the figures for trypsin and amylase, since the quantitative determination of lipolytic activity is much less accurate than the method of determination for tryptic and amylolytic power.

Discussion. In reviewing the experimental work on the relationship of the spleen and pancreas it is apparent that the researches and their results fall into two categories: first, that in which digestive experiments have been carried out *in vitro* with infusions of pancreas and spleen, and second, that in which the activity of pancreatic juice has been ascertained before and after splenectomy in animals with permanent pancreatic fistulas. In the first category the findings in most instances have been positive, and an increase in the proteolytic power of pancreatic infusions accrued from the addition of splenic extracts; in the second the results have been uniformly negative.

The explanation of this inconsistency may lie in several factors. When the proteolytic digestive power of pancreatic infusion is

tested with the addition of infusion of spleen many uncontrollable and as yet little understood elements are introduced. The spleen itself, as shown by Hedin, contains proteolytic enzymes, one acting in an acid medium and the other in an alkaline medium. It is doubtful whether these are of much importance in this connection. Of much greater significance probably are the unavoidable effects of bacterial contamination of the infusions leading to the activation of trypsinogen, as shown by Prym, and the influence of the high leukocyte content of the spleen, as suggested by Silvestri. Delezenne found a substance in leukocytes which could transform trypsinogen into trypsin, although its existence was later denied by Bayliss and Starling and by Hekma, who showed that enterokinase is produced only by intestinal mucous membrane. Opie states that the polymorphonuclear neutrophilic leukocytes and their ancestral granulated cells produce a ferment, leukoprotease, which, acting best in an alkaline or neutral medium, is similar to trypsin, though of much less activity. It is possible that this enzyme may play a part in such experiments as those under discussion. The whole question of the digestive effects of splenic extracts is surrounded by haziness, and the only definite statement to be made here is that splenic extracts should not be used therapeutically when more conclusive methods are available.

Permanent pancreatic fistulas furnish the means of approaching the problem of the relation of the spleen to the pancreas in a manner free from the drawbacks mentioned. All published investigations conducted with such fistulas have been negative. The present inquiry on the whole confirms these previous researches and justifies the statement that the spleen plays no part in the elaboration or activation of the proteolytic pancreatic ferment, trypsin.

Summary. The so-called Schiff-Herzen hypothesis in its final form assumed that during the digestive congestion of the spleen a substance is liberated into the blood stream which transforms the zymogen of the pancreas into active trypsin. Many experimental investigations have seemed to substantiate this theory; many others have seemed to invalidate it. The former have been digestive tests *in vitro* with the use of pancreatic and splenic infusions; the latter have been experiments on animals with permanent pancreatic fistulas.

In the present study data are given concerning the pancreatic secretion, before and after splenectomy, on two dogs with permanent pancreatic fistulas secreting an inactive proteolytic juice; and on two similar nonsplenectomized dogs serving as controls. Removal of the spleen in these instances caused no constant changes in the amount, enzyme content, or alkalinity of the pancreatic juice.

It is concluded from a review of the literature and this experimental inquiry that a definite trypsinogenic function of the spleen has not been demonstrated.

BIBLIOGRAPHY.

1. Badano, F.: La digestione pancreatica dell' albumina nelle lesioni della milza. Osservazioni sperimentale. Clin. med. ital., 1900, **39**, 109–122.

2. Bayliss, W. M., and Starling, E. H.: The Proteolytic Activities of the Pancreatic Juice. Jour. Physiol., 1904, **30**, 61–83.

3. Bellamy, H. F.: On the Role Played by the Spleen in the Pancreatic Digestion of Proteids. Lancet, 1900, **2**, 1185–1190.

4. Bellamy, H. F.: On the Agents Concerned in the Production of the Tryptic Ferment from its Zymogen. Jour. Physiol., 1901, **27**, 323–335.

5. Besbokaia, Menia: Du rapport fonctionnel entre le pancréas et la rate. Lausanne, Waechter-Gutzwiller, 1902, 58 pp.

6. Bufalini, G.: Sull' attività digerente del pancreas negli animali smilzati. In his: Rendic. d. richerche sper. eseg. nel Gabinetto fisiol. d. r. Univ. di Siena. Siena, Bernardino, 1879, pp. 35–54.

7. Camus, L., and Gley, E.: A' propos de l' action de la rate sur le pancréas. Compt. rend. Soc. de biol., 1902, **54**, 800–802.

8. Carvallo, J., and Pachon, V.: De l' activité digestive du pancréas des animaux à jeun, normaux et dératés. Compt. rend. Soc. de biol., 1893, **5**, 641–645.

9. Carvallo, J., and Pachon, V.: Expériences sur le pouvoir digestif du pancréas dans l' état de jeûne chez les animaux normaux et dératés. Arch. de physiol. norm. et path., 1893, **5**, 633–640.

10. Corso, F.: Il pancreas degli animali smilzati digerisce? Imparziali, 1878, **18**, 193, 257, 298.

11. Delezenne, C.: Sur la distribution et l'origine de l'entérokinase. Compt. rend. Soc. de biol., 1902, **54**, 281–283.

12. Duncan, D.: La chymie naturelle ou l'explication chymique et mecanique de la nourriture chez l'animal. Montpellier, 1683. Quoted by Gachet.

13. Ewald: Ueber Digestion mit Pankreas nach Milzextirpation. Arch. f. Anat. u. Physiol., 1878, p. 537.

14. Ferré, G.: Influence de la rate sur l'action digestive du suc pancréatique. Bull. Soc. d' anat. et physiol. de Bordeaux, 1890, **11**, 238–240.

15. Frouin, A.: Influence de l'ablation de la rate sur la digestion pancréatique chez des animaux agastrés. Compt. rend. Soc. de biol., 1902, **54**, 418–419.

16. Frouin, A.: La rate exerce-t-elle une action sur la transformation intra-pancréatique du zymogène en trypsine. Compt. rend. Soc. de biol., 1902, **54**, 798–800.

17. Gachet, J.: Du rôle de la rate dans la digestion pancréatique de l'albumin. Bordeaux, 1897.

18. Gachet, J.: Digestion tryptique des albuminoïdes dans le duodénum de chiens normaux et dératés. Gaz. hebd. d. sc. méd. de Bordeaux, 1897, **18**, 486–488.

19. Gachet, J., and Pachon, V.: Existance et nature de la sécrétion interne de la rate à fonction trypsinogène. Compt. rend. Soc. de biol., 1898, **5**, 364.

20. Gachet, J., and Pachon, V.: Nouvelles expériences sur la sécrétion interne de la rate à function pancréatogène. Arch. de physiol. norm. et path., 1898, **10**, 363–369.

21. Gersten, A.: (Part of the Spleen in the Formation of Albumin Ferment of the Pancreas.) Vrach, 1901, **22**, 1–6.

22. Gley, E.: Sur la signification de la splénectomie consécutive à l'extirpation totale de l'estomac. Compt. rend. Soc. de biol., 1902, **55**, 419–421.

23. Gutschy, L.: (The Influence of the Spleen on the Pancreatic Juice.) Liecc. viestnik. u. Zagrebu, 1898, **20**, 376–378.

24. Hedin, S. G.: Investigations on the Proteolytic Enzymes of the Spleen of the Ox. Jour. Physiol., 1903–1904, **30**, 155–175.

25. Heidenhain, R.: Beiträge zur Kenntnis des Pankreas. Pflüger's Arch. f. d. ges. Physiol., 1875, **10**, 557–632.

26. Heidenhain, R.: Herman's Handbuch der Physiologie, 1883, **5**, 206.

27. Hekma, E.: Ueber die Umwandlung des Trypsin-Zymogens in Trypsin. Arch. f. Anat. u. Entwicklungsgesch., Physiol. Abt., 1904, pp. 343–365.

28. Herzen, A.: Sulla digestione dell'albumina effetuata dal succo pancreatico e sulla funzioni della milza. Imparziale, 1869, **9**, 641, 738; 1870, **10**, 97. Also transl. (Abstr.): Cong. med. de toutes les nations, Bologne (1869), 1870, **2**, 387–392.

29. Herzen, A.: Della funzione digestiva della milza. Imparziale, 1877, **17**, 321, 353.

30. Herzen, A.: Neue Versuche über den Einfluss der Milz auf die Bildung des weissverdauenden pankreatischen Saftes. Centralbl. f. d. med. Wissensch., 1877, **15**, 435.

31. Herzen, A.: Nouvelles experiences sur le rapport fonctionnel entre le pancréas et la rate. Arch. de physiol. norm. et path., 1877, **4**, 792–794.

32. Herzen, A.: Ueber den Einfluss der Milz auf die Bildung des Trypsins. Arch. f. d. ges. Physiol., 1882–1883, **30**, 295–307.

33. Herzen, A.: Rate et pancréas. Compt. rend. Soc. de biol., 1893, **5**, 814–817.

34. Herzen, A.: La fonction trypsinogène de la rate. Interméd. de biol., 1897–1898, **1**, 266.

35. Herzen, A.: Rapport sur les fonctions de la rate. In Schiff: Ges. Beitr. z. Physiol., 1898, **4**, 232–235.

36. Herzen, A.: Rôle trypsinogène de la rate. Cong. internat. de méd., 1900, sect. de physiol., pp. 108–114.

37. Herzen, A.: Aelteres, Neues, and Zukünftiges über die Rolle der Milz bei der Trypsinbildung. Arch. f. d. ges. Physiol., 1901, **84**, 115–129.

38. Herzen, A.: Nouvelle phase de la question concernant les rapports functionnels entre rate et pancréas. Rev. méd. de la Suisse Rom., 1904, **24**, 548–552.

39. Inlow, W. D.: The Spleen and Digestion. Study I. The Spleen and Gastric Secretion. Am. Jour. Med. Sc., 1921, clxii, 325-348.

40. Inlow, W. D.: A Technic for the Formation of a Permanent Pancreatic Fistula Secreting Inactive Proteolytic Ferment. Jour. Lab. and Clin. Med. 1921, vii, 86-90.

41. Levier, E.: Sécrétion interne de la rate. In Schiff: Ges. Beitr. z. Physiol., 1898, **4**, 366.

42. Lionti, G.: Sul modo di comportarsi della secrezione pancreatica ed epatica negli animali smilzati. Riforma med., 1904, **20**, 1381.

43. Lombroso, U., and Manetta, P.: Influenza della milza sulla funzione pancreatica. Policlinico, 1915, **22**, sez. med., 117–129.

44. Lussana, F.: Intorno all'azione digerente del succo pancreatico sugli albuminoide e intorno a'le funzioni de'la milza. Ann. univ. di med., 1868, **205**, 416.

45. Lussana, F.: Della funzione digestiva della milza. Gazz. med. ital. lomb., 1877, **4**, 331.

46. Malassez, L.: Sur le pouvoir digestif du pancréas chez les chiens dératés. Gaz. méd. de Paris, 1881, **3**, 145.

47. Mendel, L. B. and Rettger, L. F.: Experimental Observations on Pancreatic Digestion and the Spleen. Am. Jour. Physiol., 1902–1903, **7**, 387–404.

48. Opie, E. L.: Inflammation. Harvey Lectures, Philadelphia, Lippincott, 1909–1910, pp. 207–208.

49. Pawlow, I. P.: The Work of the Digestive Glands. (Trans. by W. H. Thompson.) London, Griffin & Co., 1910, pp. 164–165.

50. Popielski, L. B.: [The Spleen and the Albumin Ferment of the Pancreas.] Vrach, 1901, **22**, 138–142.

51. Prevost, J. L., and Batelli, F.: Expériences relatives au rôle de la rate dans la digestion pancréatique de l'albumine. Rev. méd. de la Suisse Rom., 1901, **21**, 124–127.

52. Prym, O.: Milz und Pankreas. Versuche an Hunden mit permanenter Pankreasfistel. Arch. f. d. ges. Physiol., 1904, **104**, 433–452.

53. Prym, O.: Milz und Pankreas. 2 Teil. Versuche mit Infusen beider Organe. Arch. f. d. ges. Physiol., 1904, **107**, 599–620.

54. Prym, O: Milz und Verdauung. Verhandl. d. deutsch. Kong. f. innere Med., 1911, **28**, 398–401.

55. Rusca, C. L.: Contributo sperimentale allo studio dei rapporti tra milza e digestione. Gazz. med. ital., 1912, **63**, 321, 331, 341.

56. Sajous, C. E. de M.: The Internal Secretions of the Pancreas and Spleen. Internal Secretions and Principles of Medicine. 9 ed. Philadelphia, F. A. Davis Co., 1920, **1**, 362–420.

57. Schiff, M.: Ueber die Function der Milz. Schweiz. Ztschr. f. Heilk., 1862, **1**, 201, 397.

58. Schiff, M.: Sulle funzioni del pancreas e della milza. Imparziale, 1865, **5**, 115–117.

59. Schiff, M.: Fonctions de la rate. Cong. période. internat. d. sc. méd. Compt. rend., 1878, pp. 47–49.

60. Schiff, M.: Ueber die Funktion der Milz. Ges. Beitr. z. Physiol., 1898, **4**, 167–222.
61. Schiff, M.: Pancreas et rate. Recueil des memoires physiologiques. Lausanne, Benda, 1898.
62. Schindeler, T. A.: Beiträge zur Kenntnis der Veränderungen des thierischen Organismus nach Milzextirpation. Greifswald, Hache, 1870, p. 30.
63. Silvestri, T.: Sulla funzione tripsinogena della milza. Riforma med., 1901, Pt. I, **17**, 843, 854, 868.
64. Silvestri, T.: Sulla pretesa funzione tripsinogena della milza. Riforma med., 1902, Pt. IV, **18**, 554–558.
65. Tiberti, N.: Osservazioni microscopiche sulla secrezioni pancreatica negli animali smilzati. Sperimentale. Arch. di biol., 1903, **57**, 758. Also transl.: Microskopische Untersuchungen über die Sekretion des Pankreas bei entmilzten Tieren. Beitr. z. path. Anat. u. z. allg. Path., 1904, **36**, 184–191.

THE SURGICAL ASPECTS OF DISEASE OF THE BILIARY TRACT.

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Inflammatory disease of the gall-bladder—cholecystitis and cholelithiasis—is most commonly an affection of middle age, occurring with special frequency in women and closely associated with the incidence of pregnancy. Many cases probably originate early in life and persist with no or only vague and indefinite symptoms until some time later; manifestations are known to occur in very young children, as shown by the collected statistics of Montgomery and Wolf, and Friedenwald and Ulmann. Such diseased conditions of the gall-bladder and bile passages may, for practical purposes, be divided into those in which gall-stone formation does not occur and those in which the occurrence of calculi in some part of the biliary system outshines by its presence those other elements of the clinical picture which perhaps have a more important bearing than the stones themselves.

As one meets these conditions on the operating table the various pathological pictures which one encounters are essentially the following:

1. Gall-bladders of a normal size and shape which show a practically normal histological structure: The contents consists of a thin light-colored bile or more rarely a viscid darker bile, together with a variable number of stones. The gall-bladder contents are very frequently bacteriologically sterile.

2. Dilated gall-bladders showing a normal or only slightly abnormal histological structure and containing a single stone, which frequently is impacted in the neck of the gall-bladder or in the

cystic duct. The contained bile is rather thin and frequently is bacteriologically sterile.

3. Large distended gall-bladders the walls of which show moderate or marked grades of atrophy, especially of the mucous membrane and muscularis: There are usually a large number of various size stones which lie loosely in a large amount of thin bile. Stones may also be present in any of the ducts.

4. Gall-bladders in which infection has taken place, containing a thin pus or more rarely a thick, creamy pus with stones: The walls of the gall-bladder are thickened and edematous and the mucous membrane is very frequently gangrenous. Abscesses may be present in the wall of the gall-bladder, between it and the liver bed, or, more rarely, in the substance of the liver a short distance away. The stones contained in the gall-bladder may be numerous, indicating that conditions correspond to Groups 1 and 3, with an added infection, or only a single stone is present, indicating that a hydrops, as described in Group 2, has become secondarily infected. In all of these the cystic duct usually becomes shut off. Stones may be present in any of the ducts.

5. Gall-bladders which have shrunken to less than their normal size, and the walls of which show a chronic productive inflammation, frequently with areas in which the evidences of a more recent inflammatory reaction is discernible. The amount of pericholecystitis varies from a minimum to an excessive degree, in which it seriously hampers the necessary operative manipulations. The contents of the gall-bladder may consist only of stones or bile, which may or may not be purulent, or of both of these; or thick emulsions of cholesterin containing fragmentary stones are present. When the cystic duct is open and a probe can be passed into the hepatic and common ducts the condition represents the end-results of Groups 1, 2 and 3; when the cystic duct is obliterated the condition is the end-result of Group 4. It very rarely happens that the scarring and contracture has advanced so far that only a short stump represents the gall-bladder; such a finding represents a very near approximation to a natural cure, but only when no calculi are present in any part of the biliary apparatus.

6. Gall-bladders corresponding to any of these groups, and with which there is associated a swelling of the head of the pancreas; this includes the acute and chronic forms of pancreatitis.

7. Inflammatory gall-bladder conditions without the formation of calculi. The group includes the acute and chronic forms of catarrhal cholecystitis and the acute and chronic empyemata of the gall-bladder, both of these with and without various degrees of pericholecystitis. In the acute cases bacteria can usually be cultivated from the wall or from the contents of the gall-bladder.

8. Gall-bladders corresponding in structure to those in Group 5, but without stone formation. These represent the end-results of those in Group 7.

In any or all of these groupings the available knowledge indicates that the biological sequence of events may be one of three:

1. The pure infections indicated best in Groups 7 and 8. The element of any metabolic disturbance cannot enter unless there is a complicating non-calculous obstruction of the common duct. The affection begins as a catarrhal cholecystitis, progresses rapidly to suppuration or subsides more or less incompletely; when repeated recrudescences of infection are permitted the lesion terminates in the contracted and shrunken gall-bladder of Group 8.

2. The cases that orginate in some disturbance of the cholesterin metabolism. Most often these are initiated by the physiological changes which accompany pregnancy. The hypercholesterinemia of pregnancy may reach to such a degree as to make futile the normal compensatory mechanism; then the supersaturation of bile with cholesterol bodies is reduced to the normal by a precipitation of stones in some portion of the bile passages, almost always the gall-bladder. If no further hypercholesterinemic crisis occurs, or if no infection supervene, these patients have symptoms which are due to the mechanical effects of the stones acting as foreign bodies.

3. Combinations of infection and disturbed cholesterol metabolism may occur either simultaneously or alternately, and with different degrees of severity: Depending on the factor which is paramount, on the intensity of the latter's manifestations, on the stage of the process, or on the presence or absence of the many complicating factors, which now become numerous, the pathological picture shows wide variations.

It must seem quite apparent and beyond argument that a careful consideration of the various pathological pictures portrayed in this communication must show that, once infection of any kind establishes itself in the gall-bladder—especially as is most often the case when stones are present—the resultant lesion is there to stay and that some mechanical means is necessary before it can be entirely eradicated. The various pictures are but stages of one another and the progression of the latter from the simpler to the more complex is but a matter of time and opportunity. Anatomical healing is rarely if ever complete, and most of the attempts toward its consummation result in increasing mechanical deformity which precludes the possibility of a natural and permanent relief of symptoms. And if the focus of infection be allowed to persist for any undue length of time its evil potentialities are quickly to be noted in neighboring organs, and the end-results include additional dangerous and sometimes unrelievable lesions, and are associated with increasing risks which attend an attempt at surgical relief.

Some newer studies have shown that associated changes are present in the liver itself. One sees this clinically in the easily palpable, enlarged, engorged, congested and edematous livers. Graham

has shown that in cases of acute and subacute cholecystitis there is constantly present the evidences of inflammation characterized by a leukocytic infiltration of the interlobular and periportal sheaths; in the more severe cases the infiltration extends to the peripheries of the lobules, and is associated with edema, slight grades of necrosis and moderate fatty degeneration. Organisms were quite commonly cultivated from the liver tissue. In chronic cholecystitis the liver often presents a picture practically identical with that of an early cirrhosis. The inflammatory reaction appears to be principally a pericholangitis. One can see the basis in these findings for the persistence of infection in the liver, and in some instances, undoubtedly, this state of affairs causes a recurrence of symptoms after an apparently successful operation. The stones which come from the intrahepatic ducts—intrahepatic cholelithiasis—are most probably due to a persisting bacterial infection of the ducts and liver parenchyma.

The finding of lesions resembling those demonstrable in the early stages of cirrhosis is of particular interest, inasmuch as it indicates the possibilities with long-continued and neglected foci of disease. The studies of Ogata indicate that these may be the response to the bacterial element of the clinical picture and those of Rous and Larrimore that they may result from obstruction of the biliary drainage system. In human pathology it is very probable that both of these factors functionate; commonly stasis of bile is associated with bacterial infection and the formation of connective tissue in the liver parenchyma will be much enhanced thereby. In intrahepatic cholelithiasis a form of biliary cirrhosis is quite common.

There is considerable evidence also that the pancreas is secondarily involved in neglected cases of disease of the gall-bladder and bile passages. Infection travels very easily along the lymphatics from the primarily involved biliary tract to the pancreas and the various forms of chronic pancreatitis are probably a response to bacterial toxins as they spread within the confines of the pancreatic gland. The spread of infection from the biliary tract is first along the lymphatics of the gastro-hepatic omentum to the lymph nodes along the upper border of the pancreas and then to the gland itself. If the attacks of cholecystitis or cholangitis should be allowed to continue and repeat themselves chronic changes in the pancreas ought to be expected. The lesions in the pancreas are not limited to these chronic forms of inflammation: it is a fairly common experience to witness the hyperacute emergency of a fulminating acute pancreatitis resulting from the impaction of an apparently insignificant calculus in the ampulla of Vater—a frequently fatal lesion which might have been entirely prevented if the original condition in the biliary tract had been previously corrected by operation.

There are other important and dangerous lesions which can result from neglected gall-bladder disease. These, while not very frequent, are still common enough to be serious menaces, and in any large hospital experience one sees several of these every year. The danger of a free perforation of an acute empyema of the gall-bladder is not slight, and although in the majority of the cases the process is walled off so that only a pericholecystitic abscess results, occasionally these protective adhesions are absent and a general peritonitis of a most violent form results. It is no uncommon thing for a large gall-stone to ulcerate through the gall-bladder wall into an adherent viscus; among the difficulties that then ensue the most formidable is a stubborn infection of the bile passages which, aside from the dangers of the actual operation or operations is usually sufficient to finally cause a fatality. All of these can be prevented entirely if the underlying gall-bladder disease be recognized at an early stage and submitted to operation.

For all of us, and especially for the internist and general practitioner, the most important question must necessarily be: How shall gall-bladder disease be diagnosed at an early stage—early enough to obviate completely all of the unnecessary complications which can occur when the focus of disease is not eradicated in time? There is, unfortunately, no method of precision available at present with which this purpose can be accomplished except in a deplorably minor number of instances. One must therefore rely on the general manifestations and on those elicitable data which by their presence are presumptive evidence of gall-bladder disease.

Of all the available data the history is most important. The value of the history is very great in all disease referable to the upper abdomen and becomes predominant in disease situated in the gall-bladder and bile ducts. The clinical groups can be segregated as follows:

1. Cases in which there are one or more attacks of gall-bladder colic separated by periods of good health. Very frequently the first attack occurs in pregnancy or early in the postpartum period. The clinical picture is sharply demarcated and should be apparent even to the tyro.

2. Cases in which these attacks punctuate a constant condition of ill-health the manifestations of which, were it not for the definite attacks of colic, would be vague and indistinct and of no special discomfort to the patient.

3. Cases of dyspepsia in which the bulk of the symptoms is referred to the stomach. When as in the previous groups there are distinct attacks of acute or subacute colic it is easy to recognize that there are reflex relationships to the gall-bladder and that disease of the latter is primarily at fault; but in the others

these tell-tale marks of gall-bladder disease are not present and other evidence is necessary to make the proper diagnosis.

4. Cases in which the chief complaint is right-sided abdominal pain of no special severity and bearing the characteristics of no special symptom-complex. The clinical picture has marked resemblances to the complexes associated with dislocated kidneys in young neurotic females; to that of some of the chronic forms of appendicitis; frequently to that of ureteral stone; to other forms of intra-abdominal disease or to purely functional states. Diagnosis is always difficult in these patients and frequently is only decided at an exploratory laparotomy. To the observant medical mind these various clinical pictures differ essentially in the presence or absence of definite attacks of biliary colic typical of that accompanying the attempted or consummated passage of a gallstone down in the cystic or common ducts. When these attacks are present and are observed by a competent practitioner, or when their description as given by the patient tallies accurately with our notions of what a gallstone colic should be, they furnish indubitable evidence of the presence of disease in the gall-bladder or bile ducts—perhaps the most important single piece of evidence of any which can be obtained.

5. A fifth group of cases includes those in which a single acute inflammatory condition appears in the upper right abdominal quadrant, characterized clinically by a sudden onset with generalized abdominal pain rapidly localizing in the right hypochondrium, with nausea and perhaps vomiting, with rigidity and tenderness and most frequently with a palpably enlarged, distended and tender gall-bladder. These are the acute empyema cases having marked similarities to acute appendicular attacks and with all the necessity which the latter have for early if not immediate operation. Necessarily these must not be associated with the presence of stones, and such pure infections, especially in men, form a very common variety of gall-bladder disease.

6. The sixth group includes those cases in which, besides the usual manifestations of some acute condition in the right hypochondrium, there is added the manifestations of a general infection; these are the cholangitis cases. The clinical picture includes chills and high fever, marked prostration and other signs of a high grade of intoxication; sometimes it is possible to cultivate bacteria from the blood stream. The very acute cases carry a grave prognosis and are frequently fatal; or the process assumes a less virulent and more subacute form, and is part of the picture of the more neglected varieties of disease of the biliary apparatus. The very acute forms are uncommon and are also known to occur as operative infections; the subacute and chronic forms are relatively more frequent. In the latter it is quite probable that the actual process does not extend very far beyond the major divisions of the

primary hepatic branches in the majority of patients. The chronic forms of cholangitis ultimately become associated with new connective-tissue formations, suggestive of a biliary cirrhosis.

The evidence obtained by physical examination of the patient is second in importance in the diagnosis of disease of the gall-bladder and bile ducts; the possible data may be of two kinds: (*a*) Entirely negative, or (*b*) partially or definitely positive. The definitive data which are obtainable are the presence of a palpable mass (gall-bladder), the local and general signs of peritoneal inflammation and the presence of jaundice. When this elicitable evidence is of a positive nature it is almost always so decisive as to make unnecessary any further examination of any kind in order to establish a diagnosis; this is most liable to occur in the acute cases. In the chronic cases the physical examination is disappointting in that it usually adds no data of any kind.

The laboratory evidence which is useful in the diagnosis of gall-bladder disease is that furnished by the roentgenological examination of the patient. But positive findings are, unfortunately, neither the rule nor very common, even when other obtainable evidence is conclusive. A liberal estimate of the positive findings seems to be in the neighborhood of 25 per cent, although in the literature the claims of various workers put the positive results as high as 90 per cent. Except in these fortunate instances the laboratory evidences yield no help whatsoever.

The method devised by Lyon, of Philadelphia, is still in an experimental stage; the method holds promise. But much more work is still necessary to remove what sources of error are still present in order to put the method upon a basis reliable enough for general use in practical medicine.

To anyone who sees the actual pathology of disease of the gall-bladder and bile ducts exposed on the operating table day after day as outlined in this communication, it seems futile to say other than that these diseases are essentially surgical and susceptible of cure only by surgical means; medical treatment can at best be only palliative. And if the lesson can be learned, especially by the medical men who naturally see these cases first, of the great necessity of operating upon these patients at the earliest possible period of the disease—and that means as soon as possible after the diagnosis has been established—very much can be accomplished in a preventive way. Those who have opportunities of seeing the late results with their many unnecessary complications—and these are no uncommon things even now—need very little urging to bring their patients early to the surgeon; and the rest should learn by the experience of these others that the best way of curing the serious complications in the liver and pancreas, and the most efficient way of lowering the risks of any operative intervention, is by their total obviation in an efficiently done operation at an early period of the malady.

One should not be led astray by the enthusiasm of Lyon as regards the value of the intraduodenal use of magnesium sulphate as a therapeutic measure. The method is naturally limited and useless in cases in which the cystic duct is obstructed by calculus, by inflammatory adhesions or by extraneous masses, such as enlarged lymph glands or tumors; or in states of hydrops, or when a mass of inspissated bile or calcareous material completely fills the gall-bladder. Cholelithiasis, or acute, inflammations leading to acute and chronic empyema with or without gangrene, or any condition of a more complicated nature than the simplest, are entirely beyond the reach of this method. For such conditions the method, at best, can exhibit only slight degrees of palliation. Perhaps the only application of this therapeutic measure will be found in states similar to catarrhal jaundice.

The question as to the best form of surgical treatment for gall-bladder and biliary tract disease not only resolves itself into a discussion of the indications and contraindications of cholecystectomy as against those for cholecystostomy, but also into a discussion of the value of some form of biliary drainage. As a rule the long list of indications that one commonly observes in the literature, for which cholecystectomy is required, reads like a *resume* of the various pathologies to which the gall-bladder and biliary ducts are subject. To recapitulate these, cholecystectomy is indicated:

1. For acute and chronic empyemata of the gall-bladder, or for gangrenous gall-bladders, or for any gall-bladder inflamed to such an extent that complete restitution to the normal is not likely or even possible.

2. For hydrops or any similar condition in which a stone is impacted in the cystic duct, stricture formation in the duct, which is almost sure to follow, will prevent the permanent closure of any fistula.

3. For chronically inflamed gall-bladders with or without stones or for those thickened to such a degree that collapse of the wall is not possible to the extent of permitting a spontaneous closure of any fistula resulting from a cholecystostomy.

4. In cholelithiasis even when the gall-bladder wall shows very little or no pathological change.

5. For malignant conditions.

There is one further indication which increasing experience has shown both to include and outshine every other indication for cholecystectomy. There is constantly increasing evidence of the fact that a much superior permanent result is obtained in any instance in which a cholecystectomy is done as opposed to cholecystostomy, so that the best opinion at the present time is that a gall-bladder which is diseased enough to give sufficient symptoms to warrant an operation is one of little or no value, or is a menace to the patient's future health by reason of its potentialities for

trouble and should always be entirely removed. This restricts the usefulness of cholecystostomy markedly and its field is found in certain associated conditions, such as pancreatitis. Here the indication is drainage of bile, but even this can be accomplished through a choledochotomy opening.

It is true that in any of the cases cholecystostomy may be unavoidable, because of its supposed lesser shock and operative risk as an emergency measure—let it be emphasized—not because of the essential nature of the pathology, but because of the enfeeblement due to age or associated disease or to the deterioration of the general resistance powers due to neglected primary or complicating conditions brought to operation at a comparatively late period. Under such conditions cholecystostomy is only a palliative measure. There is much evidence to prove the statement that in competent hands the manipulations necessary for cholecystectomy under ordinary conditions, and in the average run of cases, are not so very much more productive of shock than those necessary for cholecystostomy; what difference there is, is probably due to lessened resistance on the part of the patient, and whatever little added risk is present is more than compensated for by the very great superiority of the more permanent result.

The operation of cholecystectomy fulfils a double purpose:

1. It removes a local focus of infection. When the latter is strictly limited to the gall-bladder this can be completely done and the effect is permanent. In the cases, however, in which the focus of infection has spread beyond the limits of the gall-bladder itself, either into the ducts or perhaps into the liver substances, surgical removal of the entire infected area is not feasible or possible, and a complete cure follows only when efficient drainage is adequately carried out.

2. It removes the biliary reservior with its contained stones and stagnated, infected and changed bile. The latter represents part of the end-products of any disturbed metabolism which may have antedated the operation; there is no effect upon the metabolic activities themselves. In order to obtain any effect upon the latter it is necessary to institute bile drainage either by leaving the stump of the cystic duct open (an inefficient method) or by making an additional opening into the common or hepatic ducts (a most efficient method).

The operation of cholecystostomy accomplishes the following objects:

1. Bile drainage is a necessary concomitant and sequel to this operation; hence, cholecystostomy enables a better removal of the end-products of disturbed metabolism. Practically this results in a depletion of the cholesterol content of the blood (Wilensky and Rothschild) and is a beneficial effect upon the metabolic activities.

2. Cholecystostomy affords a surgical method, inferior to chole-

cystectomy for draining the infected area. This does not presuppose that the focus of infection in the gall-bladder has been removed, and apparent healing may take place before this source of infection has completely disappeared. Recrudescences of infection may therefore be expected and do actually occur; they form one of the important causes for the recurrence of symptoms after operation.

The escape of bile through a common duct biliary fistula is always complete for a variable length of time until the subsidence of inflammatory swelling and some dilatation of the duct permit a certain amount of bile to trickle into the duodenum; clinically this is demonstrated in the color of the stools. On the other hand the escape of bile through a gall-bladder fistula is complete only when there is associated a complete obstruction of the common duct or papilla of Vater, so that between these two common-duct drainage is much more efficient.

The effects of bile drainage have been summarized by Wilensky and Rothschild as follows:

1. With common-duct drainage the system is rapidly depleted of the accumulated products of an abnormal metabolism.

2. Gall-bladder drainage does not accomplish this extreme effect unless there be a concomitant obstruction in the common bile duct.

3. These effects are only obtained when the operation is properly done and all obstructions have been removed.

The good effect of bile drainage upon a disordered metabolism is probably in the nature of a recuperative process, founded upon the removal of abnormal amounts of excretory products; this seems to have marked similarities to the phenomena of fatigue and rest in muscle tissue associated with the accumulation and discharge of excretory bodies produced by cellular activity.

To these effects may be added:

4. Bile drainage is also an invaluable adjuvant in the control of any focus of infection in the intrahepatic biliary apparatus. For this purpose it is frequently necessary to continue it for many months' time.

The continued loss of bile from a biliary fistula has a deleterious effect upon the body. The symptoms that are likely to appear include: (*a*) Disturbances of digestion frequently associated with vomiting; (*b*) constipation of varying degrees due to an absence of bile from the intestinal tract; (*c*) depreciation in the general condition of the patient conducive to a lessened general resistance to any kind of trauma. These effects may be prevented by collecting the escaping bile and feeding it to the patient by the stomach tube.

The drainage of bile is one of the most important factors in any operation upon the gall-bladder and bile ducts. We have

all learned to value the procedure extremely highly. To recapitulate: it decreases the engorgement in the liver; it depletes the body of any associated products of disturbed liver metabolism and exhibits a beneficial effect upon these activities; it is the only method we have for overcoming any retained focus of infection in the liver; what is more, it covers up and rectifies any fault of technic in the removal of stones and enables the spontaneous discharge of small intrahepatic calculi as these pass downward into the extrahepatic ducts; and what is most, by virtue of all of these it prevents many recurrences of symptoms and many secondary operations.

No drainage of any kind following cholecystectomy has been advocated by a number of men. Willis and Bottomley have published experiences with this technic. The disuse of drainage means and presupposes a careful dissection and separate ligation of the cystic duct and vessels and of a careful and painstaking aseptic technic. In this regard operative technic is repeating the experiences which were gone through in the earlier days of appendix surgery. I have referred to this refinement of technic on several previous occasions. Too little attention has been devoted to the possibility of a cleaner and safer technic in gall-bladder and common-duct surgery. This is no new practice and there is no reason why there should not be certain cases in which drainage of any form can be safely omitted. In this regard the gall-bladder has many analogies to the appendix; one does not drain every case of appendicitis, and wide experience has taught us when the drainage can be safely omitted. Experience in gall-bladder surgery is not so abundant as regards the omission of drainage, and until it is so, the insertion of a drain is perhaps a more conservative measure. I am quite sure that many times these drains are unnecessary, as evidenced by a lack of any discharge through the drainage tube and by the fact that the tubes can be safely removed at the end of twenty-four to forty-eight hours. A tube for so short a period of time in no wise delays the convalescence or the healing of the wound; certainly, it is the safest way of doing things, and the precaution would perhaps save the occasional patient that died of hemorrhage, leaking or infection.

Owing to the results of biliary infection, which is practically always present, and the fact that operation still comes comparatively late, the prognosis of interference for common-duct stone is generally unfavorable. In operating attention should first be given to the common duct, as this carries the greater urgency; attention is given secondarily to the gall-bladder if the condition of the patient and other factors permit.

Most of the literature on the surgery of the common bile duct emphasizes two points essential to a safe outcome: (*a*) That the common duct itself be well drained, and (*b*) that the abdomen be drained down to the line of suture. It has been pointed out,

and quite rightly, that the infected ducts should be drained, as infection elsewhere is drained, and that closure of the common duct is not without the danger of leakage of infected bile. The possibility of closing the incision in the common duct for the sake of securing a cleaner and safer technic has been discussed by Richter; the common duct is a suitable drainage tube in itself by which the affected parts above may be drained if its patency is assured. Under any circumstances, however, the following conditions are, according to Crile, contraindications to the closure of the opening previously made in the common duct: (*a*) If there has been a stone in the papilla; (*b*) if the duct mucosa has been so injured as to cause hemorrhage; (*c*) if there is a probability of postoperative closure of the duct by swelling; (*d*) in the event of the probability that stones will come down from the liver; or (*e*) in conditions of marked disturbance of the liver matabolism. These various contraindications do not leave a very large field in which the refinement of technic advised by Richter can be considered if one takes into account the character of these various exceptions; at least one of these indications for drainage is almost sure to occur after almost every common-duct procedure.

In competent hands the mortality of uncomplicated gall-bladder operations is very small, certainly not more than 2 or 3 per cent. With the association of complicating conditions this becomes much higher; the mortality is highest in common duct obstruction by calculus. With the latter the mortality seems to depend on the following factors:

1. The age of the patient apparently has some influence, inasmuch as most of the patients who die are over fifty years old. Van Beuren's figures showed that the operation was more dangerous in men, as shown by a 45 per cent mortality among men and an 18 per cent mortality among women.

2. I quite agree with Gibbon and others that the mortality in gall-bladder infections depends very largely on whether or not a cholangitis is present; a cholangitis is one of the real dangers of gall-bladder disease. A patient having undoubted symptoms of gall-bladder infection should not be allowed to postpone operation because of this danger; the danger, if a true cholangitis develop, is one to life; in those fortunate cases in which it does not prove fatal the convalescence is prolonged and tedious. The high mortality of gall-bladder operations occurs in the cases with long-standing symptoms, with acute exacerbations of infection and with complications.

3. The mortality has direct mathematical relationships with the length of time for which symptoms are present before operation. The longer the symptoms are present the more chance for a fatality. The immediate severity of the symptoms before operation apparently makes no difference. For the general practitioner this point is

of the utmost importance, as it shows the very great necessity of bringing patients of this type to operation at the earliest opportunity. No amount of time spent in emphasizing this extremely necessary point should be considered wasted.

4. The presence of complications—pneumonia or pulmonary congestion, chronic or acute pancreatitis, nephritis, peritoneal abscesses, myocarditis or affections of the coronary arteries—increases materially the mortality. This goes hand-in-hand with the previous statement, inasmuch as if the patients are brought to operation early many of these complications can be obviated, or at least their intensity will not be enhanced by the continued presence of the inflammatory and infectious process in the gall-bladder and biliary tract.

5. There is no doubt that the skill of the operator is an important factor in these difficult operations: the length of time of the operation, the degree of trauma, the knowledge and ability to handle the technical difficulties, are all important factors in the mortality statistics. All of these, while perhaps of little importance in the average operation, become of extreme importance in the complicated, late or neglected forms of gall-bladder and bile-duct disease.

In cases of recurring symptoms after primary gall-bladder operations sufficient to warrant secondary explorations a variety of lesions are found. The most frequently found include (*a*) adhesions of various kinds; (*b*) stone in the gall-bladder or ducts or both; (*c*) persistence of infection; (*d*) biliary fistulæ; (*e*) common-duct obstructions of various kinds, including malignancies; and (*f*) chronic pancreatitis. In some of the cases more than one of the conditions enumerated are found.

Adhesions of one kind or another are found in all of the recurrent cases. The symptom-producing adhesions are very few in number, and are principally those that result in a partial obstruction of the pylorus or first portion of the duodenum. The symptoms caused by this deformity include those of the ordinary forms of cicatricial pyloric stenosis. The simple separation of adhesions is usually followed by only temporary relief. Gastro-enterostomy, or, better still, a procedure similar to the Finney pyloroplasty, is superior to the separation of adhesions in these cases. In an old case of extensive adhesions the operation of separating the latter and covering the resultant denuded surfaces is likely to be a very difficult procedure, attended with great risk of tearing the duodenum, and in some instances the colon. If a duodenal fistula result a most dangerous and difficult proposition is present with which one must deal; and in order to guard its proper repair, gastro-enterostomy with some form of unilateral pyloric exclusion is almost always advisable.

The second most common cause for the recurrence of symptoms

is the presence of stone or stones. The failure to remove all the gallstones at the primary operation is the most potent cause for the recurrence of any symptoms. It is not always easy to determine whether these recurrent stones were overloooked at operation or whether they had actually formed again after the primary operation. The impression, however, is strong that in a few instances at least, reformation has taken place. On the other hand it is not always possible at operation to clear the two primary branches of the hepatic duct. Again, as in the attempt to remove a stone or stones from the hepatic duct, one or more may be displaced upward beyond the reach of the surgeon and thus later produce common-duct obstruction, which requires re-operation. Complete and prolonged drainage after the primary operation is essential for a preventive cure, and one should not hesitate to open the common or hepatic ducts to secure it; this applies perhaps with even greater force to the recurrent cases.

The third most common cause of recurrence of symptoms is the persistence of infection. Most often this happens after cholecystostomies. Non-calculous cholecystitis is a clinical entity distinct from the type associated with the formation of stones and justifies the removal of the gall-bladder.

Cases occur also of non-calculous, non-malignant duct obstruction due to structure, to scar tissue or to ulceration. The principles involved in the treatment of these forms of common-duct obstruction are practically the same; the duct is laid open to the extent of involvement and drainage is provided in addition to whatever other procedures are found necessary. Resection of the diseased portion and end-to-end anastomosis is best; anastomosis of the proximal end of the duct with the duodenum, with or without mobilization of the latter, after the several methods proposed, is the next best operation; reconstruction of the duct after the Sullivan method is a poor third best.

Biliary fistulæ are practically all the result of stone in the stump of the cystic duct or in the common duct; the fistula can be obliterated only by removing the cause.

Chronic pancreatitis, according to Deaver, also causes post-operative symptoms; for these drainage is very essential and should be carried out for comparatively long periods of time.

Duct drainage is also indicated, and is imperative in cholangitis which results from gall-stone disease; it must be continued for a number of weeks.

It is important to know that after cholecystectomy dilatation of the extrahepatic ducts is the rule and is to be expected. In the early and late periods after operation it is not uncommon for the ducts to become suddenly hyperdistended, possibly from some unidentifiable spasm of the sphincter; a clinical picture then results resembling minutely a typical attack of gall-bladder colic

with pain, vomiting and even jaundice and fever. Sometimes it is extremely difficult to differentiate these temporary hyperdistensions from the mechanical effect of the passage of a stone. That this can occur has been proved at secondary explorations.

The great variance between recurrences after radical surgery of the gall-bladder and those that take place after conservative surgery leads to the manifest conclusion that radical treatment gives the greater prospect of a permanent cure. For the present, however, radical surgery, although it may fall short of being ideal surgery, is the best means one has of removing a pathological condition and its pernicious effects. In general most authorities agree with this viewpoint. Gall-bladders should always be removed at the time of the primary operation, as their retention in the presence of persisting infection come to represent an infected focus from which the system is intermittently flooded with toxins. If in these cases secondary cholecystectomy is refused by the patient, chronic pancreatitis may develop in addition to the chronic cholecystitis and invalidism may develop for the remainder of the patient's life.

REFERENCES.

1. Bottomley: Boston Med. and Surg. Jour., 1920, **183,** 232.
2. Crile: New York State Jour. Med., 1920, **20,** 333.
3. Deaver and Reimann: Jour. Am. Med. Assn., 1920, **74,** 1061.
4. Gibbon: Am. Jour. Med. Sc., 1918, **155,** 644.
5. Graham: Surg., Gynec. and Obst., 1918, **26,** 521.
6. Ogata: Jour. Med. Research, 1919, **60,** 103.
7. Lyons: Jour. Am. Med. Assn., 1919, **73,** 980. Am. Jour. Med. Sci., 1920, **159,** 553; 1920, **160,** 515. New York Med. Jour., July, 1920.
8. Richter: Jour. Am. Med. Assn., 1919, **73,** 1750.
9. Rous and Larrimore: Jour. Exper. Med., 1920, **31,** 609.
10. Van Beuren:
11. Willis: Jour. Am. Med. Assn., 1917, **69,** 1943; 1921, **76,** 712.
12. Wilensky and Rothschild: Am. Jour. Med. Sc., 1918, **156,** 404 and 564.

THE ETIOLOGY OF PNEUMONIA.*

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When the physician has made a clinical diagnosis of pneumonia there are several questions which immediately present themselves for solution. Is it primary pneumonia or is the pneumonia secondary to some preëxisting pathologic condition? Is it lobar pneumonia or bronchial pneumonia? How many lobes are involved?

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Finally, and in some respects the most important question of all, Which of the various bacteria are responsible for the infection?

I am aware that many clinicians will disagree with me on the relative importance of the bacteriology of pneumonia. Strangely enough, these same clinicians will admit the necessity for bacteriologic information in other infectious diseases but deny its importance in pneumonia. We are accustomed to make early and thorough examinations for the infectious agent in meningitis; we are accustomed to bacteriologic examination in dysentery and other intestinal infections. Even in endocarditis, arthritis and certain other rarer infections, we are anxious to find the etiologic agent.

Why, then, have we been so long in coming to a realization of the importance of a bacteriologic diagnosis in pneumonia? I think there are two reasons for this lack of interest: (1) Because the bacteriology of pneumonia has been one of the last branches of this subject to be worked out accurately, and (2) because there has been no specific treatment for pneumonia. Neither of these reasons, however, hold good at the present time. The various groups of pneumococcus and streptococcus have been accurately defined. Furthermore, we have a specific treatment for pneumococcus type I pneumonia and there are good reasons for believing that an efficient specific therapy will soon be worked out for the other types. Then, too, the prognostic value of a bacteriologic diagnosis in pneumonia has not been sufficiently emphasized. In respect to prognosis the microörganism present has great significance: For example, Bacillus Friedländer pneumonia is nearly always fatal. The mortality rate in pneumococcus pneumonia varies greatly with the type. As worked out by Dochez and Gillespie at the Rockefeller Institute the rate for pneumococcus type III pneumonia may be as high as 50 per cent. On the other hand, pneumococcus type IV shows a rate of only 10 to 15 per cent. A similar divergence is found in streptococcus pneumonia. Streptococcus hemolyticus pneumonia has a death-rate varying from 40 to 60 per cent, whereas Streptococcus viridans pneumonia is one of the mildest forms encountered. In our Camp Upton series the death-rate for Streptococcus viridans pneumonia was under 10 per cent.

It would appear from these figures that in many instances the type of bacterium present had a more important bearing on the prognosis in pneumonia than either the character or the extent of the consolidation. Personally, if I must have pneumonia I am indifferent whether it shall be lobar pneumonia or bronchial pneumonia, nor am I particularly concerned whether I have two lobes or three lobes involved; but I do care very much whether my infection is caused by Friedländer's bacillus or pneumococcus type IV. Furthermore, if streptococcus is the causative agent I am very anxious to know whether it is Streptococcus hemolyticus

or Streptococcus viridans. There is the difference here between 1 in 2 chances and 9 in 10 chances for recovery.

Bacteriology of Pneumonia. Practically speaking, there are only three bacteria that are commonly concerned in the etiology of pneumonia: Pneumococcus, streptococcus and Bacillus influenzæ. Friedländer's bacillus, Staphylococcus aureus, meningococcus and other microörganisms are occasionally responsible for this disease, but they constitute such a small percentage of the whole that they must be looked upon as rarities.

The pneumococcus is the usual cause of lobar pneumonia. Dochez and Gillespie have classified pneumococci on the basis of their biologic characteristics into four groups. Thus all strains of pneumococcus type I cross-agglutinate and cross-protect. The same with types II and III. Group IV is the heterogeneous or waste-basket group and is composed chiefly of unrelated strains which do not fall into the other three groups. The first three groups are known as the "fixed types" of pneumococcus. They are highly parasitic as a rule, and except for type III rarely occur in healthy mouths. The strains that compose group IV are less virulent and are frequently encountered in healthy mouths.

At the time the studies on pneumococcus types were carried out at the Rockefeller Institute the fixed types were responsible for about 80 per cent of all lobar pneumonias, the remaining 20 per cent being caused by the group IV strains. During the two big epidemics of influenza this proportion was considerably upset by the relative increase in group IV pneumonias, but it is interesting to note that during the winter 1920-1921, in 200 cases of pneumococcus pneumonia typed at Bellevue Hospital the distribution has been as follows:

Pneumococcus type I	86 cases	43.0 per cent.
Pneumococcus type II	39 "	19.5 "
Pneumococcus type III	34 "	17.0 "
Total	159 "	79.5 "
Pneumococcus group IV	41 "	20.5 "

It is clear from these figures that the disturbance in the incidence rate produced by the influenza epidemic was only temporary and that the incidence of the fixed types of pneumococcus pneumonia is the same now as it was before the epidemic of influenza occurred.

The streptococcus is the organism most frequently found in bronchopneumonia. Here, again, we must classify into the "hemolytic" and "viridans" groups. Streptococcus hemolyticus causes a severe form of lobular pneumonia very frequently complicated by multiple abscesses and empyema. Streptococcus viridans is often recovered from the small patches of terminal bronchopneumonia discovered at autopsy in cases of chronic systemic disease. Apart from this association with terminal broncho-

pneumonias, however, the Streptococcus viridans produces a very mild form of pneumonia, the mortality rate being less than 10 per cent. It is rarely complicated by empyema. It should be emphasized that both types of streptococcus pneumonia usually occur as a complication or sequel to some preceding disease or injury. During the war the hemolytic streptococcus attained such a high degree of virulence that it appeared in some instances to excite a primary pneumonia, but such cases were exceptions to the rule.

The influenza bacillus also produces a characteristic type of pneumonia, best exemplified by the nodular hemorrhagic pneumonias so frequently seen during the big epidemic. Unfortunately for the pathologist this organism rarely occurs in pure culture, so that it is often difficult to say just what part of the process is due to the influenza bacillus and what part to the other bacteria present. A study, however, of the occasional cases of pure Bacillus influenzæ pneumonia and comparative studies on experimental Bacillus influenzæ pneumonia in monkeys indicate that this microorganism is capable of setting up a bronchitis and bronchiolitis with peribronchial consolidation—in other words a true bronchopneumonia with hemorrhage and edema, sometimes succeeded in the later stages by emphysema and bronchiectasis.

The rarer forms of pneumonia will not be discussed at the present time. The Friedländer bacillus produces a typical lobar pneumonia usually fatal, fortunately rare. Staphylococcus aureus pneumonia is another unusual form, described by Chickering[1] as a purulent bronchopneumonia with abscesses. Like Bacillus Friedländer pneumonia it is usually fatal.

The Mode of Infection in Pneumonia. The pneumococcus, like most other bacteria, attacks the human host through the nose or mouth. The mere presence of virulent pneumococci in the pharynx is not sufficient, however, to excite a pneumococcus pneumonia. It is quite possible that the bacteria reach the trachea through the inspired air. Recent experiments[2] indicate that lobar pneumonia is bronchiogenic rather than hematogenous in orgin. The constant production of the disease in monkeys by intratracheal injection and the constant failure to produce it by subcutaneous or intravenous injection are believed to be conclusive evidence that infection in lobar pneumonia takes place not through the blood stream but by way of the respiratory passages. The hematogenous theory has apparently depended upon the clinical observation of cases in which the pneumococcus was shown to be present in the blood at the time of onset of clinical symptoms of pneumonia or in occasional instances before the clinical symptoms of pneumonia had appeared. That the interpretation of this observation

[1] Jour. Am. Med. Assn., 1919, **72**, 617.

[2] Blake, F. G., and Cecil, R. L.: Jour. Exper. Med., 1920, **31**, 403, 499.

as indicative of the hematogenous origin of pneumonia is incorrect, is established by the fact that in pneumonia experimentally produced by the intratracheal injection of pneumococcus the organisms have appeared in the blood stream within six to twenty-four hours after injection— frequently before clinical evidence of pneumonia or elevation of temperature have developed.

When a monkey is injected intratracheally with virulent pneumococci and killed a few hours later it can readily be demonstrated that in experimental pneumonia, at least, the initial invasion of the lung occurs somewhere comparatively close to the hilum. The earliest inflammatory changes are found here and microscopic sections taken through this region show pneumococci penetrating the walls of the large bronchi and invading the peribronchial and perivascular lymph spaces. Furthermore, sections from the same lungs taken nearer the periphery show no pneumococci in the lumina of the bronchioles or alveoli, but they may be present in large numbers in the alveolar walls. It is quite clear that invasion and spread of pneumococci in the lung in lobar pneumonia is by way of the perivascular, peribronchial and septal tissue and lymphatics and that the alveolar structure is primarily infected by spread of the pneumococci from the grosser framework of the lungs into the alveolar walls. With further advance of the process to the stage of hepatization, pneumococci pass out from the alveolar walls into the alveolar spaces together with the exudate. Although by no means an absolute rule, hepatization usually occurs first in the posterior and upper parts of the lower and in the posterior parts of the upper lobes. This distribution in no way precludes early extension of the consolidation as far as the pleura, since the pleura is comparatively near the large bronchi and vessels in the part of the lobe proximal to the hilum. As the disease progressses, hepatization spreads to the distal portions of the lobe until complete or nearly complete lobar consolidation has occurred.

Experiments with Streptococcus hemolyticus on monkeys[3] indicate that the mode of infection in streptococcus pneumonia is similar to that in pneumococcus pneumonia. The infection is bronchiogenic and primarily affects the interstitial framework of the lung. The reaction of the tissue to the streptococcus is different, and therefore the pathologic picture is different, but the mode of infection is apparently the same for the two infections.

Coming now to the influenza bacillus a different mechanism appears to be at work.[3] In Bacillus influenzæ pneumonia the infection travels down the bronchial tree into the bronchioles and subsequently involves the neighboring alveoli by contiguity. Influenza bacilli are present in large numbers in the bronchioles and to a less extent in the adjacent alveoli. They are rarely found in any part of the interstitial tissue, and as MacCallum has pointed

[3] Blake, F. G., and Cecil, R. L.: Jour. Exper. Med., 1920, **32**, 401.
[4] Ibid., 719.

out the lymphatics are noticeably free from involvement in Bacillus influenzæ pneumonia. This may explain why the influenza bacillus rarely invades the blood stream. The influenza bacillus lacks the invasive character possessed by the pneumococcus and streptococcus, consequently the lesions produced by this organism are local while those produced by pneumococcus and streptococcus involve extensive areas. The influenza bacillus, growing in a sense outside of the body, injures chiefly contiguous parts, probably by means of toxic substances which it secretes. The pneumococcus and streptococcus, invading the lymphatics, reach all parts of the lung and excite a massive lesion.

The Epidemiology of Pneumonia. In the United States pneumonia is an endemic disease, though it also occurs in epidemic form. The United States census for 1900 shows that more than 10 per cent of all deaths are due to some variety of pneumonia, and statistics seem to indicate that the incidence is increasing. In view of the fact that so many healthy individuals are pneumococcus carriers it was formerly assumed that most cases of pneumonia were autogenous infections. During the past few years, however, important studies on the epidemiology of pneumonia[5] have been carried out at the Hospital of the Rockefeller Institute, the results of which may be briefly summarized here.

In a study of 398 normal individuals type I and type II pneumococcus were practically never encountered in the buccal secretions. Type III, on the contrary, was found in 11 per cent of the cases. Group IV was encountered most frequently, appearing in 27 per cent of normal salivas. In contrast to these figures the Rockefeller Institute investigators showed that in a series of 454 cases of lobar pneumonia either pneumococcus type I or type II was present in 62 per cent of the cases. Type III was present in only 13 per cent, group IV in only 20 per cent of the cases; in other words, the pneumococci most commonly found in the mouth secretions of normal individuals give rise to a minority of cases of lobar pneumonia. This appears to indicate that pneumonia due to types I and II does not arise from infection with the pneumococcus which is carried in the mouth, but that infection with these organisms occurs from without.

A study was also made of the types of pneumococcus present during convalescence in pneumonia. This study revealed the fact that only in exceptional instances does one find for a considerable time after recovery the same type of pneumococcus with which the individuals was infected during the disease. Usually the infecting organism was found to have disappeared in three or four weeks after the illness. After its disappearance either no pneumococcus is present or the infecting type has been supplanted by one of the types usually found in normal saliva. These obser-

[5] Stillman, E. G.: Jour. Exper. Med., 1916, **24**, 651; ibid., 1917, **26**, 513.

vations afford still further evidence that infection in pneumonia occurs from without.

Pneumococcus Carriers. Carriers of virulent pneumococci probably play an important part in the dissemination of the disease. The Rockefeller Institute workers showed that a considerable percentage of persons intimately associated with patients suffering from pneumonia harbor in their mouths pneumococci of the same type as those in the patient. Whereas pneumococcus types I and II are almost never found in normal salivas, it was shown that in a large series of healthy individuals in contact with cases of lobar pneumonia 13 per cent were pneumococcus type I carriers and 12 per cent pneumococcus type II carriers. It was also shown that pneumococcus is more frequently present in the dust of rooms in which pneumonia has occurred than in those in which no pneumonia has existed. Moreover the type of pneumococcus found in the dust corresponds to the type of pneumococcus found in the patient.

All that has been said in regard to the epidemiology of pneumococcus pneumonia probably applies with equal force to Streptococcus hemolyticus pneumonia. Although the hemolytic streptococcus is often found in normal tonsils, it is reasonable to suppose that it exists there in a comparatively harmless form. The epidemics of streptococcus pneumonia are probably caused by a few strains of virulent streptococcus which are passed on from one case to another by carriers or by actual contact. The contagious character of erysipelas, tonsillitis, puerperal fever and scarlet fever (probably a streptococcus infection) all support the idea that in streptococcus pneumonia as it existed for example in the army camps, the disease is transmitted from man to man by direct or indirect contact.

Methods of Making a Bacteriologic Diagnosis in Pneumonia. The bacteriologic examination of the sputum can be accurately made in many cases by direct plating of the material on blood agar. This method, however, is slow and for that reason undesirable. The mouse method is undoubtedly the quickest and at the same time the most reliable method of determining the type of organism in pneumonic sputum. By this method a positive diagnosis can usually be made in twelve to eighteen hours. 0.5 cc of washed sputum emulsified in sterile normal salt solution is injected intraperitoneally into a white mouse. If pneumococcus is present an agglutination test can be performed at once on the peritoneal exudate and the type determined. If the infectious agent be streptococcus or Bacillus influenzæ, or even Friedländer's bacillus, the mouse exudate will indicate it, for the peritoneum of the mouse is an ideal culture medium for all of these bacteria.

The Krumwiede method of examining the sputum is quick and reliable, but gives information only concerning the three fixed types of pneumococcus.

The Avery method is accurate when one uses very clean sputum in which the pneumococcus is present in practically pure culture. Unfortunately specimens of this character are not often obtained.

When sputum is not obtainable the diagnosis of pneumococcus types I, II and III pneumonia can sometimes be made very promptly by a precipitin test on the urine. Positive reactions, however, are usually obtained on severe cases only.

Other and less frequently available methods of making the diagnosis are by blood culture, lung puncture, examination of pleural and spinal fluid, etc. Examination of the sputum, however, remains the method of choice.

General Remarks. An accurate bacteriologic examination of the sputum is necessary before serum treatment can be rationally applied. If pneumococcus is demonstrated the type must be determined. If pneumococcus type I is present the administration of type I serum is to be seriously considered. The value of serum treatment has not yet been demonstrated for the other types.

In case Streptococcus hemolyticus is present the physician must watch the circulation and be on guard for abscess and empyema. On the other hand if nothing but Streptococcus viridans is present in the sputum, the prognosis is excellent. The influenza bacillus will only rarely be found in pure culture, but its presence in large numbers should be considered significant. In such cases there is danger of slow resolution and chronic bronchitis with occasionally emphysema and bronchiectasis.

In cases in which resolution is delayed the sputum should always be searched for tubercle bacilli. In cases of relapse a complete retyping is indicated, as relapses are often infections by a different microörganism.

The time has come when medical men should think of pneumonia in terms of the causative agent rather than in terms of anatomy or pathology—important as the latter aspects of the disease are. In consideration of the facts above presented, it would seem that the character of the infectious agent in pneumonia were more significant than the location or the type of consolidation. It is difficult at best to make accurate distinctions between lobar and lobular pneumonia, or to say in every case just how many lobes are involved in the process. On the other hand we now have at our disposal accurate and rapid methods for the determination of the infecting organism in pneumonia, and these methods are available to all practitioners, certainly to all practitioners in the larger cities. Would it not therefore be a step in advance to speak less of lobar and bronchial pneumonia and more of pneumococcus, streptococcus and Bacillus influenzæ pneumonia? The writer believes that progress in the specific treatment of pneumonia is in large measure dependent upon the adoption of such a point of view.

THE INTRODUCTION OF ANTIMENINGOCOCCUS SERUM BY CISTERN PUNCTURE. REPORT OF A CASE OF MENINGOCOCCUS MENINGITIS IN AN INFANT AGED FOUR MONTHS CURED BY THIS METHOD.*

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AND

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As much as the employment of Flexner's serum has helped to reduce the mortality and lessen the number of sequelæ in meningococcus meningitis, nevertheless the death-rate is still high and residual injury occurs in a definite percentage of cases. Anyone who has witnessed such end-results of cerebrospinal infection as hydrocephalus, idiocy, paralysis, blindness and deafness will welcome any procedure which offers promise of lessening these consequences of infection in the ventricles and subarachnoid space.

There are several causes for the failure of serum treatment of meningococcus meningitis. Thus the particular strain of meningococcus acting as the infective organism in a given case may not be represented in the serum used; the virulence of the organism may be so great that the serum is of no avail; the serum may be given late in the course of the disease when the destructive processes already present would result in the death of the patient or in permanent brain injury, even though the causative organisms were destroyed. These sources of failure have been pointed out by Ayer.[1] It must be remembered that antimeningococcus serum operates chiefly as a bacteriolytic agent and must be brought into contact with the organisms it is intended to destroy. Herein lies the explanation of many failures of serum treatment.

It would seem, then, that there are three ways by which the treatment of meningococcus meningitis might be improved: (1) By making serum which will be as polyvalent as possible; (2) by administering serum early in the infection; (3) by so introducing serum that it will be brought into better contact with the causative organisms. In this connection it might be well to speak of the fact that serum may be given intravenously. Indeed, it has been claimed that almost 70 per cent of the cases of meningococcus meningitis show evidence of generalized infection and that

* Read before the Section on Medicine of the College of Physicians of Philadelphia, November 28, 1921.

[1] Arch. Neurol. and Psychiat., 1920, **4**, 529.

the mortality can be greatly reduced by combining intravenous with intraspinal serum treatment.[2]

Our concern in this presentation is with the mode of introducing serum into the subarachnoid space. Heretofore there have been two points of entrance to the cerebrospinal system—between the lumbar vertebræ and through the fontanelle into the ventricles. Except for rare accidents, lumbar puncture has been without danger, and serum introduced by this route is curative in many cases. Subarachnoid block and the consequent failure to obtain fluid by lumbar puncture has been the indication for ventricular puncture. Ventricular puncture with the introduction of serum has increased the percentage of cures and also is apparently harmless if properly performed. After the closure of the fontanelle the ventricular point of attack is complicated by the fact that trephining is necessary. Some clinicians have gone so far as to recommend that ventricular puncture and the introduction of serum into the ventricles should be employed as a routine method in infants whenever the diagnosis of meningococcus meningitis is made.[3]

As has been stated, the chief cause of failure when serum is given in the lumbar region of the spinal cord has been the inability, at times, to bring it into contact with all the infected surfaces of the subarachnoid space. It is in such cases—when the subarachnoid space is blocked by exudate, whether in the spinal canal, the cisternæ, the foramina or over the convexity of the brain surface—that ventricular puncture has been indicated and that cistern puncture will also be found of use.

There are reasons why cistern puncture would be a method of choice if it could be shown that it is, if not devoid of danger, at least as safe as lumbar or ventricular puncture. Ayer after performing forty-three punctures in 20 cases believes that it is a harmless procedure if carefully carried out. The greatest amount of exudate in meningitis is often at the base of the brain in the cisternæ. It is from adhesions in this region that communicating hydrocephalus develops,[4,5] and it is probable also that the internal type of hydrocephalus may be caused by the spread of exudate and adhesions from the cisternæ into the foramina rather than from the ventricles into the foramina. By injection into the cisternæ magnæ the serum, in concentrated form, is brought directly into contact with the most infected portion of the subarachnoid space without the necessity of traversing the spinal canal or passing from the ventricles through the foramina and thence into the cisternæ. However, while cistern puncture should quickly gain widespread

[2] Haden, R. L.: Arch. Int. Med., 1919, **24,** 514.
[3] Caussade, L. and Remy, A.: Paris méd., 1921, **11,** 129.
[4] Blackfan, K. D.: Am. Jour. Dis. Children, 1919, **29,** 525.
[5] Dandy, W. E.: Johns Hopkins Hosp. Bull., 1921, **22,** 67.

use as a method of treatment in subarachnoid block, it will not be adopted as a regular route of approach in treating meningitis until its safety and efficacy have been further tested.[6]

The technic as described by Ayer[7] is as follows: "The patient is placed on the side, as if for lumbar puncture, with the neck moderately flexed. Care is taken to maintain the alignment of the vertebral column to prevent scoliosis and torsion, and in cases in which comparative pressure readings are important the lumbar and cisterna needles should be on the same horizontal plane. After antiseptic preparation of the skin, usually including the shaving of a little hair and local anesthetization with procain, the thumb of the left hand is placed on the spine of the axis and the needle inserted in the midline just above the thumb. The needle may be pushed rapidly through the skin, but should then be cautiously and guardedly forced forward and upward in line with the external auditory meatus and glabella until the dura is pierced.

"If the cisterna be entered at this angle there is usually a distance of from 2.5 to 3 cm. between the dura and the medulla, as shown on frozen sections; with the needle less oblique in position the distance between the walls of the cisterna becomes progressively less. Therefore it is good practice to aim a little higher than the auditory meatus, and if the needle strikes the occiput, to depress just enough to pass the dura at its uppermost attachment to the foramen magnum. At its entrance the same sudden 'give' is felt as in lumbar puncture.

"The needle employed is a regular lumbar puncture needle, nickeloid, 18 gauge preferred, with bevelled stylet, sharp on the sides but not too sharply pointed. There is rather less variation in the depth of the tissue traversed than in the lumbar region, being in an ordinary-sized adult 4 or 5 cm., the greatest distance in the series being 6 cm. and the smallest 3.5 cm. It was found that a faint circular scratch on the needle, 6 cm. from the tip, was entirely satisfactory in judging the distance, and was preferable to the deeper markings of the Patrick needle, which tend to make its insertion a little jerky and consequently less guarded."

In infants and children there are some slight modifications of this technic. Thus the distance from skin to cisterna is somewhat less—being about 2.25 to 3.5 cm., depending on the age of the patient. A needle smaller than 18 gauge may be necessary at times, although a fairly large caliber needle is preferable to allow for the flow of thick and viscid cerebrospinal fluid. It has seemed to us that the "give" of the needle on entering the cisterna magna is greater than that which is experienced in successful lumbar puncture, and one should be cautious not to exert too much

[6] See discussion of Dr. Ayer's paper in Arch. Neurol. and Psychiat., 1920, **4**, 465-469.

[7] Loc. cit.

pressure, lest the sudden entrance of the needle carry it too far in a forward direction.

While cistern puncture has been done on animals [8 9] and for obtaining material at autopsy for some time, its use in the living human subject has been reported only by Wegeforth,[10 11] Ayer and Essick. It might be said in passing that the cistern has been drained after trephining at the base of the skull for the relief of meningitis.[12]

We wish to put on record our experience with cistern puncture in a case of meningococcus meningitis. Previous to the employment of cistern puncture in this case we had carried out the procedure on the cadaver with and without the skull-cap removed, and also in several cases of tuberculous meningitis. In this latter condition the usual temporary relief of symptoms of increased intracranial pressure was noted exactly as would occur after lumbar puncture. Since treating the case of meningococcus meningitis, we have used cistern puncture in a case of streptococcus meningitis and also in 2 cases of pneumococcus meningitis, but then only for diagnosis.

CASE REPORT. J. B., Italian, male, aged four months. Admitted to the Children's Hospital of Philadelphia, service of Dr. J. P. Crozer Griffith, March 15, 1921. On admission the infant was partly breast-fed and partly artificially-fed with a cow's milk mixture. Throughout the entire illness this combined feeding was continued.

History of Present Illness. For two weeks prior to admission the patient had been apparently in a febrile state, although the temperature had not been taken to verify this statement of the mother. The baby did not seem very ill until five days before admission, and the fever before this may have been due to a left otitis media, which had been discharging at times for about six weeks. Three days before admission convulsions, described as generalized, began, and these had recurred at frequent intervals since that time. The exact number of convulsions could not be determined, but they were evidently of frequent occurrence, as well as of different grades of severity.

No history of the symptoms other than those enumerated above could be elicited. There had been no vomiting or other gastro-intestinal disturbance. The absence of vomiting is to be remarked, since this symptom is one of the earliest and most constant signs of meningitis, being in our experience more frequent than convulsions.[13] The child seemed drowsy between the convulsive

[8] Dixon, W. and Halliburton, W.: Jour. Physiol., 1913, **47**, 215.
[9] Weed, L.: Jour. Med. Research, 1914, **31**, 21.
[10] Wegeforth, P.: Ayer, J. B. and Essick, C. A.: AM. JOUR. MED. SC., 1919, **157**, 789.
[11] Loc. cit.
[12] Haynes, I. S.: Arch. Pediat., 1913, **30**, 84.
[13] Mitchell, A. G. and Falkener, W. W.: New York Med. Jour., 1918, **107**, 103.

seizures, but nursed from the breast and bottle fairly well. The mother was not intelligent enough to have noted such conditions as hyperesthesia or rigidity. The past medical history, including the details of the patient's birth, was uneventful, the patient having been born at full term by easy labor.

On admission the baby seemed quite sick. The temperature was 101° F., the pulse 150 and the respiration 48. Examination of the heart, lungs and abdomen revealed no abnormal findings. There was, however, marked retraction of the head as well as a positive Kernig sign in both legs and other evidences of cerebrospinal irritation, such as increased knee-jerks, a positive Babinski reflex on both sides and a definite Brudzinski sign. A suggestive tache cérébrale was present. No ankle-clonus could be elicited. Pus was discharging from the left external auditory meatus. The pupils were equal and reacted slightly to light. The fontanelle was not bulging or tense—in fact, there was a slight depression in this region. Lumbar puncture performed at this time was unsuccessful, as fluid was not obtained.

March 16. On this date lumbar puncture resulted in obtaining only 2 cc of a very thick, yellowish fluid which showed the meningococcus in the stained smear, and later the organism was found on culture by Dr. A. G. Waltz. After the removal of the fluid 1 cc of antimeningococcus serum was introduced with difficulty.

March 17. The first convulsive seizure since admission occurred on this date. By lumbar puncture 1.5 cc of thick pus were obtained. After irrigation of the spinal canal with physiologic sodium chloride solution, 1.5 cc of antimeningococcus serum were introduced.

March 18. During all this time the physical findings described on admission were present and the fontanelle remained depressed and under normal tension. Because of the evident subarachnoid block and the absence of a bulging fontanelle it was decided to do cistern puncture rather than ventricular puncture. A needle introduced after the manner described by Ayer at first failed to obtain fluid. A stylet was introduced into the needle. When the stylet was withdrawn it was followed by a long string of material resembling nothing so much as tenacious nasal mucus. Immediately after this a stream of turbid spinal fluid flowed from the needle under considerable pressure; 9 cc of this fluid were removed and 6 cc of antimeningococcus serum were then slowly introduced. The specimen obtained by cistern puncture showed the meningococcus on smear and culture; contained albumin and globulin in large amount; had 2900 cells to the cm. and did not reduce boiling copper solution.

March 19. Lumbar puncture was not successful in obtaining fluid. By cistern puncture 17 cc of turbid fluid were removed under marked pressure; 5 cc of serum were introduced. A few

hours after the cistern puncture the patient had convulsive twitchings of the face and extremities.

March 20. Twelve cc of cloudy fluid were obtained by cistern puncture and 8 cc of serum were introduced.

March 21. Rigidity was still present, although not as marked as on admission. The fontanelle continued to be slightly depressed. Vomiting of a projectile character occurred for the first and only time while the child was under observation. On this date also it was noticed that the sclera of the left eye was injected. Subsequently the left eye developed panophthalmitis. Permission to remove the eye was refused and the condition eventually subsided with a subsequent atrophy—the right eye fortunately remaining normal. (The eye had been examined and treated by Dr. H. M. Langdon and Dr. A. R. Renniger.)

March 22. Eight cc of almost clear fluid were obtained by cistern puncture and 6 cc of serum were introduced. No meningococci were found in this fluid.

March 24. On this date it was decided to try lumbar puncture again, with the result that 7 cc of somewhat blood-tinged fluid were obtained under slightly increased pressure. No serum was given. A cistern puncture was then done. After the removal of 2 cc of clear fluid, which did not seem to be under increased pressure, the patient suddenly became shocked—the respiration ceasing for almost fifty seconds and the pulse being practically imperceptible. The needle was immediately withdrawn and the return to a normal pulse and respiratory rate was rapid.

March 26. Six cc of clear fluid under normal pressure were obtained by lumbar puncture. No serum was given. No meningococci were found.

April 15. By this time the baby's general condition had greatly improved. There was still slight rigidity of the neck, but other signs of cerebrospinal irritation were not present. No puncture had been performed since the one in the lumbar region on March 26.

April 26. The patient was discharged on this date, cured of meningococcus meningitis. There was atrophy of the left eye and a shrunken condition of the tissues of the orbit.

Six months after discharge from the hospital the patient was seen and examined. With the exception of the atrophy of the left eye the cure was apparently complete and no evidence of cerebrospinal irritation, optic atrophy, hydrocephalus or paralysis could be found.

We have reported this case because we desire to call attention to the applicability of cistern puncture to infants, and because, as far as we have been able to ascertain, this is the first case of subarachnoid block due to the meningococcus which has been cured by cistern puncture.

REPORT OF A CASE OF DISSEMINATED GUMMATOUS SPOROTRICHOSIS, WITH LUNG METASTASIS.*

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Diseases due to certain varieties of fungi are claiming more and more attention. Scattered through the literature are many case reports and careful bacteriologic investigations of actinomycosis, blastomycosis, streptothricosis, sporotrichosis, etc. Some of the fungus diseases are primarily pathogenic for animals, and only now and then produce disease in man when conditions are favorable. Many of the forms of fungi occasionally pathogenic for man are, in their natural state, saprophytes on dead vegetables, bark of trees, hay, etc. Gradually the various forms have been differentiated one from another until now there are numbers of well-recognized mycelium-bearing fungi which may cause even fatal disease in man. Among these Gougerot gives an important place to the sporotrichum. In an address delivered in 1913[1] he gives six reasons why sporotrichosis should claim attention:

1. Because of its extreme frequency (in France, at least) and of its universal distribution. There is no part of the civilized globe which has not had its case or cases. In France over 200 cases were reported in the literature from 1906 to the end of 1910. Since then no one reports his cases unless there is something unusual about them.

2. Because of the practical importance from both prognostic and therapeutic standpoints of a correct diagnosis. He cites a number of cases in which the patients were given several months to a year rest-cure under the diagnosis of pulmonary tuberculosis. In 1 case reported a man had had a hip-joint amputation, then a forearm amputation was advised but refused. Diagnosis was corrected and the patient was well in six weeks. One case had severe pharyngeal ulcerations which were thought to be syphilitic. Mercury had been given, with no relief. Diagnosis was finally corrected and the patient was soon cured.

3. Because of the polymorphism of the disease there is no tissue exempt from its ravages, including bone.

He makes three main groups with subgroups:

I. Disseminated sporotrichosis.

(*a*) Disseminated gummatous non-ulcerating variety of the skin.

* Read at the Meeting of the Association of American Physicians, Atlantic City, May 10–11, 1921.

[1] Gougerot: Sporotrichosis, Jour. State Med., London, December, 1913, **21**, 705–768.

(*b*) Subcutaneous ulcerating tuberculoid gummata.
(*c*) Ulcerating syphiloid gummata.
(*d*) Polymorphous sporotrichosis.
II. Localized sporotrichosis.
III. Extracutaneous sporotrichosis—osseous, ocular, visceral, etc.

4. Because of the great ease in diagnosis one does not need a laboratory nor does he need to be an expert bacteriologist. He does need, however, tubes of glucose-agar. By inoculating a tube with some of the purulent material in the ulcers or abscess and placing it aside at room temperature for four to ten days the microscopic appearance is characteristic.

5. Because of the almost certain healing of even the most extensive lesions by the internal administration of KI, necessitating no loss of time by the patient from his daily occupation.

6. Because in the intensive study of the disease a new impetus was given to the study of mycotic diseases in general.

The honor of calling attention to the pathogenicity of the sporotrichum goes to B. F. Schenck,[2] of Johns Hopkins, who in 1898 published an article in the *Bulletin of the Johns Hopkins Hospital* on "Refractory Subcutaneous Abscesses Caused by a Fungus Possibly Related to the Sporotricha." He isolated and grew out the organism which has since been known by the name of Sporothrix Schenckii. In 1900 Hektoen and Perkins published a long article on the sporothrix. The first case published in any other country was that by de Buermann in 1903. Four years elapsed with the report of only 4 cases seen by de Buermann and Gougerot, then the *Bulletin et mémoires de la Société medicale des hôpitaux de Paris* was full of reports. From that time cases have been reported from various countries and from most of the states in the United States. Hyde and Davis,[3] of Chicago, reported on the disease in 1910.

In 1912, Ruediger[4] was able to collect 57 cases from the American literature. Only 24 of these were culturally proved cases. There was one brief report of a probable case from northern Wisconsin. An analysis of the cases revealed that the largest number from any single state was from North Dakota and that most of the cases occurred along the valley of the Missouri River.

Sutton[5] had previously reported a case, and within a year 11 cases had been reported from the Missouri Valley.

[2] Bull. Johns Hopkins Hosp., 1898, **9**, 286.
[3] Sporotrichosis in Man, with Incidental Consideration of its Relation to Mycotic Lymphangitis in Horses, Jour. Cutan. Dis., July, 1910, **28**, 321. (Complete bibliography to date, including the articles published during 1907 and 1908 in Bull. et mem. Soc. méd. d. hôp. de Paris.)
[4] Sporotrichosis in the United States, Jour. Infect. Dis., 1912, **11**, 193.
[5] Sporotrichosis in the Mississippi Basin, ibid., 1914, **63**, 1153.

Haynes and Cheney reported the first case in West Virginia in 1914.

Blaisdell,[6] in 1917, reported the first case in New England. None have been reported since, although cases must have been seen since then,

The sporothrix has been found in every tissue of the body. The common type in this country is the localized lesion. Following an injury a nodule appears, often on the tip of a finger, ulcerates and discharges pus. Healing is very slow or does not occur. Within a short time a nodule forms along the lymph channels which drain the part and the lymph vessels become cord-like. Farther up another nodule forms, connected with the first by an indurated line of tissue slightly or not at all reddened. Others may form along the same line, so that a chain of several separate nodules may be seen along the arm or leg. They may ulcerate and cicatrize or become soft and break down with ulceration. Frequently if the nodules are close together the tissues are undermined and a probe may be passed in the subcutaneous tissue from one ulcer to another. As a rule there is not much tendency to spontaneous healing. The ulcers may last for weeks or months. The course is usually very slow. There are no disseminated gummatous lesions reported in this country.

In France especially there have been many widespread subcutaneous nodules and ulcerating forms reported. However widespread the lesions, they always begin as a firm, usually painless but sometimes very tender nodule in the subcutaneous tissue. In the disseminated form every nodule is separate and no cord-like tissue links it to its nearest fellow. After growing to a variable size the skin over the nodule becomes purplish, especially at the apex, and quite thinned, and fluctuation is felt. The nodule breaks, releasing a sanguinopurulent material. There is little or no zone of inflammation around the base of the nodule. The resulting ulcer has a punched-out appearance resembling so much a syphilitic ulcer that many errors in diagnosis have been made. The ulcer may show signs of healing, the base becomes clean and healthy granulations appear, while the epithelium grows in from the periphery. While some may be healing other nodules and ulcers are forming.

Although de Buermann and Gougerot stated, in 1907, that the regional lymphatic glands do not enlarge, this is not altogether true. They do not show the same tendency to become involved as do the glands draining tuberculous or syphilitic skin lesions, but they do enlarge and even become tender in many cases.

De Buermann and Gougerot, in 1907, reported the thirteenth case. This was an ascending gummatous lymphangitis located

[6] A Case of Sporotrichosis; First Case in New England, Jour. Cutan. Dis., 1917, **35,** 452.

on the arm of a man, aged fifty-seven years. It was the first case of the kind reported in France. A period of eighteen months elasped between the appearance of the first and second abscess. In this case the axillary glands were not enlarged. That the course of the lymphangitis is not always as described above is shown by the case of Dominici and Rubens. The initial lesion was the result of a finger-cut. Later there were numerous scattered subcutaneous gummata on the arm without lymphangitis and without swelling of the lymph glands.

De Buermann and Gougerot saw a sporotrichal chancre of the forehead.

Alvin and Vallin[7] report a case of a large abscess and fistula in the brow of a woman, aged fifty-one years.

Daulos and Blanc report a case of palpebral sporotrichosis.

Wilder[8] reports conjunctival ulceration, culturally proved, in a laboratory assistant who was working with cultures of the sporothrix, and frequently capillary tubes were broken within ten inches of his eye.

Morax reports a most unusual case of uveal sporotrichosis with secondary episcleral lesions and absence of all other discoverable sporotrichal localizations.

De Buermann and Gougerot reported the first case of sporotrichosis of the pharyngeal mucous membrane. The organism was grown from the ulcer and also from the apparently intact mucous membrane.

Letulle and Klebré, in the course of a report on a case of sporotrichosis of the skin, mouth, pharynx, larynx and trachea in which the whole posterior buccal cavity was a shallow ulcer, say that the sporothrix buermanni can live an indefinite time in a saprophytic state.

Monier-Vinard and Gaucher, in 1907, reported the first case where the sporotrichum was grown from the sputum.

Widal and Weill reported, in 1908, a case of disseminated sporotrichosis with periosteal lesions in which the sporotrichum was recovered from the circulating blood. Widál and Abrami also showed at this time that the spores of the sporotrichum were agglutinated by the blood of patients affected with the disease in dilutions of 1 to 800. The blood serum of a patient with actinomycosis agglutinated the sporotrichum in dilutions of 1 to 150. Complement fixation with the spores as antigen has also been described.

The disease usually begins as a local lesions at the site of some injury. The fact that the fungus lives as a saprophyte on all kinds of vegetables and dead matter and bark of trees makes it strange that the infections among humans are so few. Some curious

[7] Sporotrichosis, Lyon médical, October, 1920, **129**, 859.
[8] Sporotrichosis of the Eye, Jour. Am. Med. Assn., 1914, **62**, 11.

sources of infection have been reported. Thus, Sutton reports a case due to a hen-bite, Rouslacroix to a parrot-bite and others to bites of horses.

Olson[9] reported a case of the lymphangitic form in a man from North Dakota who had killed and handled many gophers, many of which had sores similar to those on the patient's hand. Many cases began from the crushing of a finger-tip and from cuts while in hay fields. Several cases are reported by the French of disseminated type in which no portal of entry could be found. The patients were vegetable venders and the organism was found on the vegetables.

Meyer[10] thinks that flies may act as passive carriers. In horses, dogs and rats in this country sporotrichosis is found spontaneously.

Davis[11] found that a small epidemic among horses on a farm in North Dakota which was thought to be farcy was sporotrichosis. The disease was also found among horses in Pennsylvania. Bovines do not seem to be susceptible to the disease but the hides may act as transmitters of spores (Meyer).[12]

All the American cases, with few exceptions, which I have been able to find have been of the lymphangitic type. A case reported by Ravogli,[13] in 1913, had a huge tuberculoid ulceration around an elbow.

Hyde and Davis's case was apparently the gummatous form. Le Blanc[14] has recently briefly recorded 2 cases of what had been thought to be pulmonary tuberculosis. He saw a small nodule on the larynx of each one and claimed that he found spores of sporotrichum in the sputum. There were no skin lesions.

Dominguez,[15] of Cuba, reported, in 1914, a case in a tobacco-leaf tester who was ill with fever and with the lung findings of pneumonia. His illness was prolonged and no tubercle bacilli could be found in the sputum. By roentgen-ray plate a shadow was found in the lung. A fungus lesion was then suspected and sporotrichum was grown from the sputum. Later an abscess of the middle ear developed from which sporotrichum was grown. An extradural abscess was operated and drained, but culture was negative for the fungus. The author found sporotrichum on the tobacco leaves.

Besides these lesions cases are reported by the French of genital lesions and muscle and bone lesions, and Councilman grew a sporotrichum from the fluid of a swollen and inflamed knee-joint.

[9] A Case of Sporotrichosis, ibid., September 21, 1912, **59,** 941.

[10] The Relation of Animal to Human Sporotrichosis, Jour. Am. Med. Assn., 1915, **65,** 579.

[11] Loc. cit.

[12] Loc. cit.

[13] Report of a Case of Sporotrichosis of the Tuberculoid Type, Lancet-Clinic, Cincinnati, 1913, **110,** 112.

[14] Le Blanc, F.: Pulmonary Infection by Sporothrix of Schenck, Ill. Med. Jour., December, 1920, **38,** 516.

[15] Sporotrichosis with Multiple Localizations, Med. Rec., April 4, 1914, **85,** 608.

The case here reported is the only one of its kind recorded up to the present in the United States. The complete report of the bacteriologic, experimental and immunologic studies will be published later by my assistant, Arthur Margot.

CASE HISTORY. The case is that of a young negro, aged twenty-three years, admitted to the Milwaukee County Hospital March 8, 1920, who had followed the race horses as a stable boy in the southern and western circuits. He was born in Arkansas. Except for his journeys from New Orleans to California with the horses and a recent trip to Detroit he has always lived in the southern part of the country. He came to Milwaukee direct from Detroit and was in the city for five months before he was taken ill.

The family history is negative. As a boy he had measles, whooping-cough and mumps. When nineteen he had swollen and painful joints lasting a month, but was not confined to bed. At the age of fifteen he had both gonorrhea and an "eating chancre" without suppuration of the inguinal glands. He does not drink but smokes cigarettes to excess. He dated his present illness as far back as June, 1919, when he was ill with fever and chills, but was not confined to bed. Ever since then he has felt weak. About two weeks before admission a swelling appeared on the top of the right foot. There were no ulcerations of the toes, but the toes felt "sprung." This swelling was painful, at first hard, then later soft. It broke in about a week and yellow matter came out. It then began to heal. In the meantime nodules appeared on the top of the left foot, on both upper arms, posterior surfaces, both cheek bones and forehead. He became so weak that he entered the hospital.

Physical examination revealed a somewhat emaciated negro of medium height. On the left side of the forehead at the hair line was a soft painful swelling. There was slight dark discoloration of the skin of the nodule, and it was sharply demarcated from the surrounding skin. It measured 2 cm. in diameter and was raised about 1.5 cm. There was a rough bony edge encircling the base, as if the bone had been eroded. Behind the right ear was a tender superficial ulceration covered by a thin crust. The face was distorted by a swelling in the skin over each malar bone. One was somewhat softer than the other. On the exterior surfaces of both lower arms there were nodules, the largest measuring 3 cm. in diameter. All nodules were tender, some were discolored and others were not discolored. All showed more or less fluctuation. They appeared to be in the subcutaneous tissue. In the dorsum of the right foot there were three superficial ulcers, two of them almost healed; one measured 3 x 4 cm. and had a healthy granular base and a punched-out appearance.

There were moist rales at the bases of both lungs, more numerous

on the left side. The skin of the left posterior apex was very sensitive to palpation. The percussion note was slightly impaired and the breath sounds were a trifle harsh. No rales were heard. Over the whole left side the respiratory excursion was slightly limited and the tactile fremitus, percussion note and breath sounds were not as distinct as on the right side.

The heart was not enlarged; there were no murmurs; the rate was 90 to the minute; the pulse was soft and compressible.

The abdomen was retracted; no masses were felt; the liver and spleen were normal in size; the reflexes were normal.

There was irregular fever as high as 103° F. throughout the illness. The urine was normal at first, but later contained a slight amount of albumin, and shortly before death was full of bile pigments. The leukocytes were 17,000; the Wassermann reaction was ++++.

As soon as he was seen by me he was thought to have an infection with some one of the fungus diseases. A soft nodule was aspirated under aseptic precautions and the yellow blood-stained pus was examined fresh and cultured. A mycelial network was found which on culture proved to be sporothrix.

Suspecting that there might be some lesion in the lung a roentgen-ray plate was made and the sputum examined. Nothing of interest was found in the sputum, which was scanty.

The roentgen-ray plate showed a clear right apex and slightly hazy left apex. There was a large, somewhat circular shadow extending from the right hilum, about 6 cm. in diameter. Radiating from the edge of this were fine linear markings extending into the first interspace and outward to the edge of the outer zone. Along the left heart border was some fine spotting. The left hilum was also increased in size.

In spite of large doses of potassium iodide and of arsphenamine new nodules developed at various places on the arms and legs while those on the face were gradually healing. Over the outer surfaces of both thighs very large undermined nodules developed. Cultures made from the contents of many nodules invariably showed the same sporothrix.

On April 1, it was noted that on the inner side of the middle of the left thigh was an elongated hard nodule from which a cord-like induration extended a short distance in both directions. Shortly after this he developed intense jaundice. One nodule over the left malar bone had increased in size; the skin was thin and bluish, but there was no elevation of temperature; 10 cc of a yellow purulent blood-stained fluid were aspirated from this nodule.

The patient gradually grew worse. Many nodules were open and were draining freely. The temperature was always elevated. He died on May 23, 1920.

It was not possible to autopsy the body until June 2, 1920, ten days after death. The report of Dr. Margot is as follows:

The body is that of a large-framed but extremely emaciated male negro. The legs and arms are swathed in bandages. Upon removal there are seen huge ulcerating surfaces with undermined discolored skin, one enormous cavity occupying a large part of the outer surface of the left thigh. At the scalp margin on the brow are two punched-out ulcerations. In the skin over the right malar bone is a fluctuating tumor 4 cm. in diameter and 2 cm. above the skin level. Over the left malar bone is a similar but larger nodule. The conjunctivæ have an icteric tint. The pupils are equal but rather large. Rigor mortis is present, postmortem lividity is marked. There is no edema.

Thorax. On removing the sternum the left lung lies entirely free from adhesions but shows a slight hypostatic congestion in the posterior portion of the lower lobe. There is an area of congestion on the posterior surface of the lower lobe of the right lung. A nodule about 1.5 cm. in diameter is found in the upper right lobe having the characteristics of those found in the skin. The mediastinum contains no enlarged glands.

Heart. The pericardium and heart reveal no abnormalities except for probable softening of the muscle.

Abdomen. The abdominal fat is scanty and has a yellow color. The peritoneal surfaces are smooth and glistening. No free fluid is found.

Spleen. The spleen is slightly enlarged; the surface is smooth; color dark; consistency irregular both soft and firm. On section there are dark-red dry areas which are firmer than the rest and extend deep into the spleen. The Malpighian bodies are pretty well seen throughout the cut surface.

Liver. The liver extends 4 cm. below the costal border. It is mottled and the external surface is smooth. It is firm. On section it drips blood. The cut surface is somewhat glistening and the cut edges roll over and the markings are indistinct.

Kidneys. The kidneys are slightly increased in size and are firm. The capsule strips readily from both. Typical cloudy-swelling markings are seen with a swollen cortex.

Gall-Bladder. The gall-bladder is distended and contains about 45 cc of purulent exudate and bile. The wall is thickened and edematous. No stones are found.

Pancreas. The pancreas appears not to be affected.

Microscopic Examination of Tissues. Owing to the fact that the body was ten days in the morgue before autopsy the tissues were more or less autolyzed. However, it was possible to obtain good specimens of the lung. Sections of the nodule in the right lung are made up of connective tissue in which are small round cells, scattered polymorphonuclear leukocytes, plasma cells and large

mononuclear cells, probably from the alveolar epithelium. The lung structure is completely obliterated. Many giant cells are present. These have irregular shapes; the protoplasm stains a uniform pink with eosin and the many apparently vesicular nuclei are arranged along the periphery of the cells, at times almost encircling the cell. The resemblance to the giant cells of tuberculous tissue is very close. There are lacking the caseous areas and the tubercle arrangement. There are many distended capillaries throughout.

The kidney sections show marked cloudy swelling with detritus in the collecting tubules. Many Bowman capsules are unusually thickened.

The liver sections show cloudy swelling and congestion of the central veins with atrophy of the liver cells for about one-third to one-fourth of the lobule.

No special changes are seen in the spleen or in a lymph gland at the hilum of the right lung.

Sections from the edge of several of the skin nodules show a connective-tissue stroma infiltrated with leukocytes, round cells and many giant cells much like those found in tuberculosis. Very few eosinophils were seen. Early stages of the nodules are made up of embryologic connective tissue infiltrated with many plasma cells and some polynuclear cells. As the nodule softens the leukocytes increase in number. No proliferation of capillaries is seen. Giant cells are found. It is often quite impossible in certain areas to differentiate these lesions from those of tuberculosis.

We grew the organism from the pus of several nodules on ordinary nutrient agar-agar in the incubator at room temperature. The best media were potato and Sabouraud's glucose peptone agar. At room temperature the growth is slow. In the incubator on agar at the end of twenty-four hours small circular colonies of silky-white appearance are seen and a dense branching, silken, whitish mycelium spreads over the surface. In tubes this penetrates vertically for a distance of 5 to 10 mm. into the depths of the medium. In addition to this adherent layer of interlacing filaments an abdundant aëreal wooly mass of filaments appears within forty-eight hours. Radiations of short filaments from the center of the growth on the agar surface are found from which fruiting hyphæ arise, at the free ends of which are sporangia. The columella, seen after the discharge of spores, projects in a spherical body from the funnel-shaped, expanding end of the supporting hyphæ. The spores are conical in shape; they are chlamydospores (Davis)[16] and measure about 4.5 micra in length, although the range is from 4 to 5 micra.

[16] Formation of Chlamydospores in Sporothrix Schenckii, Jour. Infect. Dis., November, 1914, **15**.

After four to five weeks the growth on the agar or potato appears dry and the color changes from white to mouse gray on to dark brown. De Buermann, who described the first case in France five years after Schenck had published his report, has given his name to the organism, and possibly on account of his many publications the name of the sporotrichum is more widely known under the name sporothrix buermanni than under its correct name, sporothrix schenckii. Priority, however, in this case is undisputed and the organism should be known by its original name.

It would appear that de Buermann's organism and our organism are slightly different in their pathogenicity from the one described by Schenck and the ones described by Hektoen and Perkins, Hyde and Davis and others in this country. The difference lies in the ability of the first group to produce lung lesions in albino rats, whereas no lung lesions were ever produced by any of the previously described American sporotricha. Culturally there is no essential difference. Since Davis reported that the sporothrix schenckii produced chlamydospores, that distinction of the two species no longer served to differentiate them.

It is interesting that our case, the only one reported in this country which is simi'ar to the gummatous cases reported in France, should be caused by a sporotrichum different in pathogenicity from all the reported American cases, but like that reported by the French investigators. We procured cultures from various parts of the country and injected them into rats. Our culture was the only one which produced lung lesions.

The spores alone develop and germinate in the organs of animals (Margot). An emulsion of spores was injected intravenously into rabbits, albino rats and guinea-pigs. Within ten to twelve days the animals developed cachexia, and if not killed died from the injection. Autopsy showed nodules scattered in the liver, kidney, spleen and brain. The nodules were subcapsular, deep, isolated and conglomerate. Cultures from the organs developed typical mycelium.

Only in the albino rats were lung lesions produced. Inoculation by any route invariably produced nodules in the lungs. The histologic appearance of the nodules was similar always, only varying in the proportion of giant cells and other formed elements. No spores were definitely found in the giant cells.

Our organism was agglutinated by the patient's blood (sporo-agglutination) in dilution of 1 to 150. Control sera gave no agglutination.

By using an emulsion of crushed spores as antigen, complement fixation was obtained. Unfortunately we neglected to draw blood from the living patient for culture. The result would have been interesting but of no value in diagnosis.

Summary. A case of disseminated gummatous sporotrichosis in a young colored man is reported. There was a nodule in the right lung, suspected on physical examination, seen in the roentgen-ray plate and confirmed at autopsy culturally and histologically. This is the first case of its kind reported in American literature. The sporotricha reported from American cases and some reported from French cases differ in the pathogenicity and in the ability to produce lung lesions in albino rats.

Attention is again called to sporotrichosis as a generalized disease and to the probability of cases of lung sporotrichosis which are unrecognized.

REFERENCES.

Adamson, H. G.: A Résumé of the Literature Relating to Sporotrichal Infections of the Skin, British Jour. Dermatol., 1908, **20,** 296. (All literature to date.)

Hamburger, W. W.: Sporotrichosis, Jour. Am. Med. Assn., November 2, 1912, **59,** 1590.

Hamburger, W. W.: Sporotrichosis in the United States, Ill. Med. Jour., February 1914, **25.**

Quém, E.: (Sporotrichosis of the Breast), Rev. de Chir., Paris, 1914, **34,** 553–720.

Morax: (Uveal Sporotrichosis with Secondary Episcleral Sporotrichosis; Absence of All Other Discoverable Sporotrichal Localization), Ann. d'occul., Paris, 1914, **152,** 273.

Davis, B. F.: Report of a Case of Sporotrichosis, Surg., Gynec. and Obst., 1914 **19,** 490.

Haynes and Cherry: Case of Sporotrichosis, First Case in West Virginia, West Virginia Med. Jour., 1914–1915, **9,** 303.

Wohl, M. G.: Report of a Case, Nebraska State Med. Jour., December, 1920, **5,** 355.

Brainos, A.: (Sporotrichosis of the Genital Organs), Paris médical, March, 1920, **10,** 247.

COMPARATIVE PROGNOSIS IN TUBERCULOUS LESIONS OF THE RIGHT AND LEFT LUNG. A STUDY OF 1048 CASES.

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Very few, and somewhat conflicting, are the recorded observations on the comparative prognosis of right- and left-sided tuberculous lesions and bilateral lesions in which one lung is more extensively involved. Brown[1] maintains that there is no difference in gravity between lesions of the right and the left lung. On the other hand, other observers speak of the mildness of right-side lesions in comparison with those of the left side, and point to the

less favorable prognosis in lesions of the left lung. Text-books on the subject shed but little light on this phase of pulmonary tuberculosis, and references to such investigations cannot be found in most standard works on disease of the lungs. It is evident, therefore, that this subject will stand further investigation.

In reviewing the extensive literature on therapeutic pneumothorax one is impressed with the fact that the number of left lungs collapsed is far greater than that of the right, notwithstanding that, generally considered, the left lung is less frequently involved in pulmonary tuberculosis. This would indicate a greater frequency of severe lesions in the left lung. Impressed with this occurrence, Tecon and Aimard,[2] Mark[3] and others have carefully analyzed the data at their disposal. They conclude that as the disease advances there is a great preponderance of left-side lesions, and that a tuberculous condition in the left lung is of more serious import than one in the right and demands a more guarded prognosis. Mayer,[4] Cavalcanti,[5] Strandgaard[6] and others, although unable to confirm the above observation as regard the much greater frequency of left-lung involvements in the advanced stages of phthisis, agree, nevertheless, that the prognosis is less favorable in those whose predominating lesion is in the left lung.

The 1048 cases which form the basis of this communication were observed for from five months to several years. They were all subjected to repeated roentgenological examinations, and their diagnosis was clear cut. The classification of the National Tuberculosis Association was strictly adhered to, both in regard to diagnosis on admission and condition on discharge.

TABLE I.—LUNG INVOLVEMENTS IN 1048 CASES

Right lung only.	Left lung only.	Both lungs.	
		Right lung most.	Left lung most.
326, or 31.1 per cent	152, or 14.5 per cent	344, or 32.8 per cent	226, or 21.6 per cent

The figures of Table I show that of the 1048 cases studied, 152, or 14.5 per cent, suffered from tuberculosis of the left lung only and 226 from bilateral pulmonary tuberculosis with preponderating left-side involvement, or a total of 36.1 per cent of preponderating left-lung lesions; while 326, or 31.1 per cent, suffered from right-side lesions only, and 344, or 32.8 per cent, were afflicted with bilateral lesions in which the right side was more extensively involved; or a total of preponderating lesions of the right lung of 63.9 per cent. In other words, in unilateral lesions, the percentage of right-side involvement was about 2 to 1 as compared with

the left, while in bilateral lesions there was a decided increase in the number of involvements of the left lung, so that the percentage of preponderating right-side lesions was only 3 to 2 as compared with the left.

TABLE II.—LUNG INVOLVEMENTS IN THE VARIOUS STAGES OF PHTHISIS.

		Right.		Left.	
		No.	Per cent.	No.	Per cent.
Stage I	Male	125	11.9	53	5.0
	Female	70	6.7	44	4.2
Stage II	Male	213	20.3	93	8.9
	Female	115	11.1	60	5.8
Stage III	Male	92	8.8	69	6.5
	Female	55	5.1	59	5.7
Total		670	63.9	378	36.1

Considering the various stages of the disease separately, Table II discloses the interesting fact that whereas in the first and second stage of the disease the percentage of the right-side lesions is about 2 to 1 as compared to the left side, the percentage of the right involvements in the third stage is not greater, but is about equal to that of the left. This is not in agreement with the figures of Tecon, Aimard and Mark, which show that in advanced phthisis the left side is much more often involved than the right. The evidence, however, points to a remarkable increase in the number of left-side lesions as the disease advanced.

TABLE III.—RELATION OF SIDE OF LESION TO ACTIVITY OF DISEASE.

	Male.				Female.			
	Right.		Left.		Right.		Left.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Inactive	285	66.3	119	56.8	128	53.4	57	41.2
Active	145	33.7	96	43.2	112	46.6	96	58.8

Analysis of Table III shows that both male and female patients in all stages of the disease whose preponderating lesion was on the left side ran an active course while at the sanatorium, more

frequently than those with preponderating right-side lesion, the ratio being 4 to 3 in favor of the left lung.

TABLE IV.—CONDITION ON DISCHARGE.

		Male.				Female.			
		Right.		Left.		Right.		Left.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Stage I	Arrested; improved	121	96.8	52	98.1	67	95.7	42	95.5
	Unimproved; progressive	4	3.2	1	1.9	3	4.3	2	4.5
Stage II	Arrested; improved	176	87.4	80	86.0	95	82.6	48	80.0
	Unimproved; progressive	37	12.6	13	14.0	20	17.4	12	20.0
Stage III	Arrested; improved	52	56.5	27	39.2	34	61.8	28	47.5
	Unimproved; progressive	40	43.5	42	60.8	21	38.2	31	52.5
	Total	430		215		240		163	

Scrutiny of the figures in Table IV discloses the fact that in early tuberculosis the prognosis is no better in right than in left apical lesions. However as the disease advances the prognosis becomes less favorable in predominating lesions of the left lung. Thus the percentage of patients discharged "unimproved" and "progressive" in the second stage in male patients is 14 per cent in predominating left-lung lesions as against 12.6 per cent with right-lung involvements, and in the females 20 per cent "progressive" in lesions of the left lung as compared with 17.4 per cent in predominating right-lung lesions. In the third stage the prognosis in left-side lesions seems to be decidedly worse than in lesions of the right lung. Here the percentage of patients discharged with condition "progressive" is 60.8 per cent in left predominating lesions as compared with 43.5 per cent in right predominating lesions among the males and 52.5 per cent "progressive" in lesions of the left lung as compared with 38.2 per cent in right-side lesions among the females, or a ratio of 3 to 2 among males and 4 to 3 among females.

Discussion. Although it is universally admitted that the minimal lesion in pulmonary tuberculosis is most frequently found at the right apex the available data do not indicate the exact proportion of right and left apical involvements. This proportion varies within a wide range, depending on the character of the investigation. There is, however, a fair agreement that as the disease advances there is a decided increase in the number of left-lung

lesions, so that when we observe a group of patients in whom the disease has reached the so-called "third stage" we find that in cases with unilateral disease the left lung is involved as often as the right, and in cases with bilateral lesions the predominating lesion is discerned on the left side no less frequently than on the right. This in itself, however, does not shed much light on the relative prognosis in lesions of either side. When, on the other hand, we look into the results of institutional treatment in all stages of phthisis we gain a definite idea as to the relative prognosis of right- and left-side lesions. Our observations are in accord with most observers, to the effect that the prognosis in early right apical lesions is no better than in lesions of the left apex. It is quite different, however, in the advanced stages of phthisis. Here it is definite that the prognosis is less favorable in cases with predominating lesions of the left lung. These patients are liable to run an active course more often than those with preponderating right-side lesions, and the percentage of these cases discharged "unimproved" and "progressive" is almost one and one-half times as large as that of cases with right-side involvement.

There seems to be some conflict of opinion as to the probable explanation of the increased gravity in left-side lesions. It is stated that the narrow caliber of the left bronchus, by interfering with the proper aëration of the left lung, favors the rapid progress of the disease once it is implanted in its upper lobe. This explanation, however, does not seem to possess the germ of conviction.

A more rational explanation for the greater gravity in left-side lesions is to be found in this: The right lung has three lobes whereas the left lung has but two. The division of the lung into lobes seems to retard the rapid spread of tuberculosis because the fissures which separate the lobes are lined with double layers of serous membranes which are more refractory to tuberculous disease than the lung tissue proper. It is evident that the right lung with two fissures is better equipped to check the rapid spread of the disease than the left, which, after the one fissure is passed, has no other barrier to retard the spread of the disease.

It has recently been pointed out that even in health, areas of atelectasis are frequently found in the left lower lobe. These are probably caused by the encroachment of the pericardium and its contents on the left lower lobe and are responsible for the marginal rales which are so often heard in the region of the left base. Sewall[7] states that "a conclusion might be plausible that the atelectatic condition distinctly favors the development of phthisis." Is it not possible that, at least to some extent, atelectasis favors the rapid spread of tuberculosis in the left lung?

There are also causes which indirectly render the prognosis of lesions on the left side more serious. Clinicians have long recognized that patients suffering from phthisis stand the dislocation of the mediastinal organs to the right much better than their dis-

location to the left. Dyspnea, cyanosis, palpitation, etc., are not often complained of in acquired dextrocardia due to fibrosis and shrinkage of the right lung, whereas the above symptoms are often met with in a distressing form in patients with sinistracardia due to advanced tuberculosis of the left lung. We see many cases with extreme dextrocardia who work and do well generally for many years, but those whose cardiac displacement is to the left have but a small cardiac reserve and seldom do well.

Shrinkage of the left lung also causes marked retraction of the left diaphragm and adjacent abdominal viscera. In some instances the retraction is so extreme that the stomach is actually pulled into the thoracic cavity and simulates a diaphragmatic hernia or localized pneumothorax.[8] The normal function of the stomach is thus materially interfered with to a much greater extent than is possible in lesions of the right side, no matter how extensive. This further aggravates the prognosis in advanced disease of the left lung.

Summary. The results of our study lead us to conclude:

1. In early tuberculosis the right side is affected twice as often as the left.

2. As the disease progresses there is a marked increase in the number of involvements of the left lung, so that in the advanced stage of the disease the right and the left lungs are numerically equally involved.

3. Patients with a predominating left-lung involvement are liable to run an active course more often than those with preponderating right-side lesions.

4. In early phthisis the side of the lung involved has no definite relation to the general prognosis.

5. In advanced phthisis the prognosis is distinctly less favorable in those with preponderating lesions of the left lung.

6. The presence of but one interlobar fissure, moderate atelectasis and the evil effects of sinistracardia and retraction of the stomach are factors which contribute toward the greater gravity of left-lung lesions as compared to the right.

REFERENCES.

1. Modern Medicine (Osler and McCrae), Lea & Febiger, Philadelphia, 1915, **1**, 461.

2. Gravité comparée des localisations tuberculeuses pulmonaires gauches et droites; Etude de 2000 cas, Rev. de la. Suisse romande, January, 1917, **37**, 45.

3. Comparative Prognosis of Tuberculous Lesions of the Right and Left Lung, Jour. Am. Med. Assn., May 10, 1919, **72**, 1348.

4. Welche Lunge erkrankt am häufigsten an Tuberculose, München. med. Wchnschr., August 6, 1920, **67**, 935.

5. Ueber die Frage der Lokalization des Lungentuberculose, Dissertation, Zurich, 1920.

6. Welche Lunge wird vorzugsweise durch Tuberkulose angegriffen, Ztschr. f. Tuberculose, 1910, **16**, 114.

7. Pulmonary Atelectasis, Am. Rev. Tuber., January, 1921, **4**, 11, 811.

8. Stivelman, B.: False Pneumothorax, Jour. Am. Med. Assn., January, 1920, **74**, 12.

OBSERVATIONS ON THE BLOOD IN CASES OF CHRONIC NEPHRITIS ASSOCIATED WITH NITROGEN RETENTION.*

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During the course of certain forms of chronic nephritis, anemia plays a prominent role in the clinical picture of the disease. Attempts have been made to correlate the anemia with the presence of edema, dilution of the blood being considered a possible explanation. Very early, von Jaksch[1] found that in chronic nephritis edema held no constant relation to the plasma content of the blood. The studies of Keith, Rowntree and Geraghty,[2] and more recently those of Bock,[3] seem to indicate that in chronic nephritis, as well as in other conditions, the plasma volume of the blood remains remarkably constant, variations in total blood volume being due to the corpuscular content. Edema does not affect the plasma volume to any appreciable extent. Ewing[4] found that severe anemia occurs in chronic nephritis, especially in cases associated with edema; but he also observed cases of severe anemia in nephritics without edema. With the introduction of more accurate methods of determining the constituents of the blood serum, and especially the nitrogen partition, Widal, Abrami and Brule[5] reported a case of severe anemia occurring in a nephritic without edema, but with nitrogen retention. Recently, Aubertin and Yacoel[6] reported two cases of chronic nephritis, with nitrogen retention, in which a severe anemia was present, making the added observation that anemia was relatively rare among cases of the non-nitrogen retention type. They collected a series of cases which demonstrated that the anemia was practically exclusively encountered in cases of chronic nephritis showing nitrogen retention and no edema.

Through the courtesy of Drs. Brill and Libman, I was enabled to study the following cases in detail:

Case I.—Mrs. I. M., aged forty-six years, married, Austrian, housewife, was admitted September 21, 1920, complaining for

* Read before the Section on Medicine at the New York Academy of Medicine, May 17, 1921.

[1] Ztschr. f. klin. Med., 1893, **23**, 187.
[2] Arch. Int. Med., October, 1915, **16**, 547.
[3] Ibid., January, 1921, **27**, 83.
[4] Clinical Pathology of the Blood, 1903, p. 414.
[5] Bull. et mém. Soc. med. des hôp. de Paris, 1907, p. 1427.
[6] Presse méd., 1920, **28**, 461.

three years of headaches, general weakness and yellowish discoloration of the skin. She had a history of "kidney trouble" fifteen years before; at that time she was ill for four months. Edema was present. Eleven years ago she had a miscarriage. The menopause occurred three years ago.

Her present illness began three years ago, with intermittent headaches of a thumping nature, most severe over the parietal and occipital regions, and radiating down to the back of the neck. Attacks of headache began suddenly, lasted twenty-four hours or longer and gradually subsided. During the attack the patient vomited, often ten to twelve times; the vomiting was not projectile. There were recurrences nearly every week. For the last three weeks the headaches have become constant but less severe; the attacks of vomiting have become less frequent.

The patient has had frequent attacks of epistaxis during the last three years. She complains of marked weakness. Her vision has been poor for the last three years. There have been no convulsions or paralyses. Three years ago she noticed that her skin was becoming progressively yellow. Her appetite has been poor; she has been habitually constipated. Her stools have never been clay colored or tarry. Hematemesis occurred on two occasions several weeks ago. Micturition four or five times daily, moderate amounts; nocturia three or four times. There has been no edema of the face or extremities. She has lost sixty pounds within the past three years. Cardiac and respiratory symptoms have been absent.

Summary: "Kidney trouble," associated with edema, fifteen years ago; a miscarriage eleven years ago; for three years had headaches associated with vomiting, weakness, yellow skin, epistaxis and blurred vision; hematemesis several weeks ago; nocturia; loss of sixty pounds in weight within the last three years.

Physical Examination: The physical examination showed a poorly-nourished, fairly well-developed woman of middle age. Her skin had a waxy yellow appearance; the conjunctivæ and other mucous membranes showed marked pallor. All the teeth were missing. There was marked distention of the jugular veins and marked episternal and supraclavicular arterial pulsations. The lungs were negative. The heart borders were not enlarged, the sounds were of fair quality; there was a soft, blowing systolic murmur at the apex, which was transmitted toward the axilla. The radial pulses were regular and equal, of moderate rate, fair force and volume; the arterial walls were thickened and tortuous. The abdomen was negative. The extremities showed no edema; the reflexes were active and equal. Over the skin of the extremities were scattered ecchymoses; there were a few petechiæ over the left breast. The cervical lymph nodes were enlarged. Vaginal and rectal examinations were negative.

Upon admission the patient's systolic blood-pressure was 235, and the diastolic 120. The urine showed a moderate amount of albumin, with a specific gravity of 1006; there were present a few epithelial cells and leukocytes. The urinary output in twenty-four hours was 600 cc. The phenolsulphonephthalein test showed less than 5 per cent excretion in two hours.

Blood Examination. September 22, 1920:
Hemoglobin, 55 per cent (Kuttner).
Erythrocytes, 2,500,000.
Hemoglobin index, 1+.
Leukocytes, 4800.
Polynuclear neutrophiles, 76 per cent.
Lymphocytes, 13 per cent.
Monocytes, 11 per cent.

Smear. Erythrocytes fairly well filled. Slight anisocytosis and poikilocytosis. No macrocytes or normoblasts seen.

Coagulation time: 8 minutes.
Bleeding time: 2½ minutes.
Fragility test: Hemolysis begins at 0.375; complete at 0.30.

Capillary resistance, hemostaxis appears in 5 minutes.

Blood Examination. September 24, 1920:
Hemoglobin, 42 per cent (Kuttner).
Erythrocytes, 2,120,000.
Hemoglobin index, 1.
Leukocytes, 4800.
Polynuclear neutrophiles, 75 per cent.
Lymphocytes, 22 per cent.
Monocytes, 3 per cent.

Smear: Erythrocytes of good shape and color. Occasional polychromatophilic macrocytes and stippled erythrocytes seen.

Two further blood determinations gave practically the same findings as the last.

Blood Chemistry. September 23, 1920:
Urea nitrogen, 54.6 mg. per 100 cc.
Incoagulable nitrogen, 126.0 mg. per 100 cc.
Uric acid, 7.2 mg. per 100 cc.
Creatinin, 4.6 mg. per 100 cc.
Cholesterin, 0.212 per cent.

Blood Chemistry. October 18, 1920:
Urea nitrogen, 123.2 mg. per 100 cc.
Incoagulable nitrogen, 180.0 mg. per 100 cc.
Uric acid, 8.5 mg. per 100 cc.
Creatinin, 11.0 mg. per 100 cc.
Cholesterin, 0.108 per cent.

The urine continued to show a moderate amount of albumin. The specific gravity varied from 1006 to 1009. The urinary output in twenty-four hours averaged one liter. The systolic blood-pressure fell to 170 and the diastolic to 100. The Wassermann reaction was negative. The Rehfuss test after the first hour showed complete absence of free hydrochloric acid; the total acidity was 20.

With the aid of colonic irrigations, forced fluids and medication she became more comfortable. After a six weeks' stay in the hospital she left against advice. The figures for the blood chemistry indicated a poor prognosis.

CASE II.—Miss Y. R., aged twenty-six years, a Roumanian, milliner by trade, was admitted February 7, 1921, complaining for six weeks of pain in the back and right side, progressive weakness and edema of the face. The family and personal histories were negative. During childhood she had measles, whooping-cough, scarlet fever and diphtheria. Eight years ago she had suffered from swelling of the face, abdomen and extremities, which gradually improved in the course of one and a half years. Three years ago she had typhoid fever. She also had influenza about that time. The patient has had occasional attacks of palpitation and dyspnea upon exertion. Attacks of sore-throat had been frequent. The menstruation had always been normal.

The present illness began six weeks before admission, with an attack of vomiting and fever, associated with pain in the right side and back. The pain was sticking in character, radiating down to the legs and up to the shoulder. It was so severe at times that it kept the patient awake at night. She claims to have noticed swelling of the face. Weakness and malaise have been very marked since the onset of her present symptoms. She has had frequent headaches, and experiences a dizzy feeling when standing. There have been palpitation and dyspnea upon exertion, associated with moderate precordial distress. She has not vomited since the original attack. Nocturia has been marked.

Summary: Infectious diseases of childhood; swelling of the face, abdomen and extremities eight years ago; typhoid and influenza three years ago; palpitation and dyspnea; pain in the back, weakness and edema of the face (?) for the last six weeks; headaches and dizziness; nocturia.

Physical Examination: The patient was a fairly well-developed and well-nourished young woman who appeared to be chronically ill. The conjunctivæ and other mucous membranes were very pale. The following were the positive findings: The facies was suggestive of myxedema rather than of a true edema of the face; the skin was somewhat thickened and had a yellowish pallor. The heart was moderately enlarged. At the apex the first heart

sound was replaced by a prolonged, soft, blowing murmur, systolic in time, transmitted toward the axilla and heard over the entire precordium. The second heart sound was of fair quality and intensity. The aortic second was louder than the pulmonic second. The radial pulses were equal, regular and of moderate tension; the arterial walls were not thickened. The lungs were negative. The abdomen was negative except for slight tenderness in the right upper quadrant. There was no edema of the extremities.

Upon admission the patient's systolic blood-pressure was 170 and the diastolic 120. The urine contained a large amount of albumin with a specific gravity of 1008; a few leukocytes were present. The urinary output in twenty-four hours was one liter. The phenolsulphonephthalein test showed no dye excretion in two hours.

Blood Examination. February 8, 1921:
Hemoglobin, 31 per cent (Kuttner).
Erythrocytes, 1,500,000.
Hemoglobin index, 1+.
Leukocytes, 5400.
Polynuclears neutrophiles, 65 per cent.
Lymphocytes, 33 per cent.
Monocytes, 2 per cent.
Smear: Erythrocytes show slight anisocytosis and poikilocytosis.

Blood Examination. February 13, 1921:
Hemoglobin, 33 per cent (Kuttner).
Erythrocytes, 1,504,000.
Hemoglobin index, 1+.
Leukocytes, 6600.
Polynuclears neutrophiles, 71 per cent.
Lymphocytes, 25 per cent.
Monocytes, 4 per cent.
Smear: Erythrocytes show slight anisocytosis and poikilocytosis.
Fragility test: Complete hemolysis, 0.200 to 0.250; partial hemolysis, 0.275 to 0.425; no hemolysis, 0.450 to 0.625.
Further blood determinations showed a progressive anemia.

Blood Examination. March 10, 1921: (The patient had frequent but slight epistaxis at this time):
Hemoglobin, 22 per cent (Kuttner).
Erythrocytes, 1,252,000.

March 15, 1921:
Hemoglobin, 20 per cent (Kuttner).
Erythrocytes, 1,120,000.

Coagulation time, 7½ minutes.
Bleeding time, 11 minutes.
Blood negative for bile and urobilin.

May 12, 1921:
Hemoglobin, 22 per cent (Kuttner).
Erythrocytes, 1,040,000.

Blood Chemistry. February 8, 1921:
Urea nitrogen, 50.4 mg. per 100 cc.
Incoagulable nitrogen, 104.2 mg. per 100 cc.
Uric acid, 6.9 mg. per 100 cc.
Creatinin, 6.0 mg. per 100 cc.
Cholesterin, 0.276 per cent.

Blood Chemistry. March 4, 1921:
Urea nitrogen, 53.2 mg. per 100 cc.
Incoagulable nitrogen, 116.7 mg. per 100 cc.
Uric acid, 4.1 mg. per 100 cc.
Creatinin, 8.5 mg. per 100 cc.

The urine continued to show a large amount of albumin. The specific gravity varied from 1004 to 1012. The urinary output in twenty-four hours averaged 1300 cc. The systolic blood-pressure dropped to 120 and the diastolic to 80. The stool gave a positive reaction to the guaiac test, and on two occasions contained ascaris lumbricoides.

The therapy consisted of the following: Forced fluids and the Murphy drip, the Karrel diet, colonic irrigations with sodium bicarbonate and hot packs.

When the patient's hemoglobin fell to 20 per cent a citrate transfusion of 500 cc was performed (April 12). Clinically she benefited markedly, her hemoglobin rising to 32 per cent. This was of short duration, however, the hemoglobin rapidly falling to 22 per cent. Her condition is growing progressively worse.

Similar to the cases reported by Aubertin and Widal these patients present two syndromes: First, a severe anemia characterized by a high hemoglobin index, relatively little change in the morphology of the erythrocytes, absence of abnormal forms in the blood and a leukopenia, and second, a chronic nephritis with high nitrogen figures and uremic symptoms.

The following data were collected to determine:

1. The relative frequency of anemia in chronic nephritis, with and without nitrogen retention.
2. Whether there was any relation between the presence of edema and the occurrence of anemia.
3. The characteristics of the anemia.
4. The etiology of the anemia.

CASES OF CHRONIC NEPHRITIS WITH NITROGEN RETENTION

Case No.	Edema.	Urea nitrogen.	Erythrocytes.	Hemoglobin, per cent.	Hemoglobin index.	Leukocytes.
I. . .	0	54.6	2,500,000	55	1.1	4,800
		123.2	2,120,000	42	1.0	4,800
II. . .	+	50.4	1,544,000	31	1.0+	5,400
		57.2	1,504,000	33	1.0+	
III. . .	+	49.0	2,228,000	50	1.1+	9,000
IV. . .	0	121.8	4,180,000	73	0.8+	
		126.0	2,900,000	65	1.1+	
V. . .	Slight	43.4	2,650,000	55	1.0+	8,000
		68.0				
VI. . .	+	107.8	2,520,000	45	0.9	
VII. . .	Slight	78.0	2,480,000	42	0.8+	12,000
			2,064,000	32	0.8	14,200
VIII. . .	Slight	54.6	2,500,000	40	0.8	7,400
IX. . .	0	71.4	2,824,000	43	0.7+	6,200
X. . .	0	154.0	2,300,000	40	0.8+	20,000
		214.2				
XI. . .	0	156.8	3,200,000	45	0.7+	8,200
XII. . .	0	140.0	3,300,000	58	0.9	14,000

CASES OF CHRONIC NEPHRITIS WITHOUT NITROGEN RETENTION

Case No.	Edema.	Urea nitrogen.	Erythrocytes.	Hemoglobin, per cent.	Hemoglobin index.	Leukocytes.
I. . .	0	18.2	5,000,000	80	0.8	8,400
II. . .	0	12.6	4,800,000	86	0.9	12,800
III. . .	+	21.0	4,800,000	94	0.9+	8,800
IV. . .	0	11.2	4,860,000	75	0.7+	9,400
V. . .	+	15.4	4,520,000	86	0.9+	5,300
VI. . .	+	18.2	4,480,000	80	0.9+	8,000
VII. . .	+	26.6	4,200,000	81	0.9+	13,000
VIII. . .	+	22.4	4,000,000	70	0.8+	18,000
IX. . .	0	28.0	4,000,000	77	0.9+	7,200
X. . .	+	25.2	4,000,000	70	0.8+	6,000
XI. . .	0	23.8	4,565,000	82	0.9	
XII. . .	+	21.0	5,000,000	90	0.9	
XIII. . .	+	12.6	3,500,000	64	0.9+	7,200
XIV. . .	−	14.0	3,480,000	84	1.2+	8,300
XV. . .	+	12.6	3,500,000	64	0.9+	7,200
XVI. . .	+	14.0	3,000,000	45	0.7+	5,000
			2,910,000	42	0.7+	

Summary: As far as possible, those cases were chosen in which one could be reasonably certain that the anemia was not secondary to some complication such as hemorrhage, parasitic infection or new growth.

A study of these cases indicates that severe anemias occur nearly exclusively in chronic nephritis associated with nitrogen retention. Cases XI and XII in this group show relatively less advanced anemias. Only single blood counts, however, were made, and

the cases were not followed up. In the non-nitrogen group, Case XVI, which shows a severe anemia with low nitrogen figures, was in an advanced condition of cachexia upon admission; the anemia was probably associated with the nutritional disturbance. There is undoubtedly a large number of cases like XIII, XIV and XV which do not fit in either group. These cases may be in a phase of transition. Though the nitrogen figures have not increased there is present a moderate anemia. In such cases the anemia may be the precursor of changes in the figures for blood chemistry.

It is of interest to note Cabot's[7] statement that in chronic nephritis (without regard to the presence or absence of nitrogen retention) anemia is a relatively infrequent finding. In a study of 64 cases he found only 12 with an erythrocyte count of two to three millions and only three with a count between one and two millions. In our series of cases the relative frequency of anemia in all types of chronic nephritis coincided, approximately, with Cabot's figures. It should be added that the erythrocyte counts in our cases did not reach the low levels reported by Cabot and Aubertin.

Edema holds no constant relation to the presence or absence of anemia. According to our statistics anemia may exist in the absence of edema, and edema may occur without an associated anemia.

The most striking feature of the anemia in the nitrogen retention group is the high hemoglobin index. In many of the cases reported in this group (I to V inclusive) the hemoglobin index is above 1; the remainder of the cases also show a relatively high index. Among the more important conditions in which a hemoglobin index over 1 is found are the following: Primary pernicious anemia, bothriocephalus infection, pernicious vomiting of pregnancy and new growths, especially bone tumors with metastases. Ewing[8] notes the fact that a high hemoglobin index occurs in the anemia of chronic nephritis. He adds that "grave or pernicious anemia develops in a small proportion of cases of chronic parenchymatous nephritis and appears, at times, to result directly from the nephritis." Blood smears in cases of chronic nephritis with nitrogen retention and a severe anemia, studied by us, were usually negative for the abnormal forms found in pernicious anemia. However a few polychromatophilic macrocytes were found in a case studied by Dr. N. Rosenthal. Further studies are needed on this point.* The erythrocytes were usually well preserved and well filled with hemoglobin; macrocytes and normoblasts were not found. The leukocytes showed no marked changes either in number or character. In Cases I and II a leukopenia was present; Cases VII, X and XII presented a leukocytosis. The

[7] Clinical Examination of the Blood, 1904, p. 365.
[8] Loc. cit.
* Many macrocytes were found in a case which was studied very recently.

differential count, except for a slight polynucleosis, was not abnormal. Myeloblasts, myelocytes and lymphoblasts were not noted. The blood picture presented by these cases is not uncommonly found in such conditions as carcinomatosis accompanied by severe anemia; in the latter form, however, abnormal erythrocytes or leukocytes, or both, are liable to be present.

It is of interest to note briefly the observations made by Aubertin and others with respect to the bone-marrow reactions in severe anemias occurring in chronic nephritis with nitrogen retention. Aubertin and Yacoel[9] report two cases, in which the blood pictures closely resemble those studied in our series; subsequent study of the bone-marrow, made by these investigators, revealed it to be macroscopically very fatty, and microscopically there was no evidence of activity. Elsewhere, Aubertin[10] reports a case of latent interstitial nephritis in which eclampsia developed. The blood picture was that found in pernicious anemia, there being present a high hemoglobin index, macrocytes, normoblasts, polychromatophilia, myelocytes and a relative lymphocytosis. The bone-marrow in this case was hyperplastic. On the other hand, Widal[11] reports a case of chronic nephritis with nitrogen retention in which the blood picture showed a very severe anemia with a hemoglobin index above 1. The blood smear showed complete absence of myeloid reaction.

The nature of the anemia in chronic nephritis with nitrogen retention, therefore, cannot be determined from the blood picture alone. Studies of the bone-marrow and spleen are necessary properly to interpret the anemia. Studies made thus far seem to suggest that the hematopoietic organs are profoundly affected in this form of nephritis.

As far as an etiologic factor is concerned nothing can be determined until more is known about the etiology of uremia. The anemia might be due to a hemolytic agent acting directly upon the erythrocytes; it might also be due to an inhibitory action by the same agent or some other unknown toxic factor upon the hematopoietic organs; a combination of both factors would possibly be responsible.

We expect to undertake investigations directed toward determining more accurately the reaction of the bone-marrow and spleen in cases of chronic nephritis associated with nitrogen retention and accompanied by a severe anemia.

Conclusions: 1. Severe anemia in chronic nephritis occurs principally in cases accompanied by nitrogen retention.

2. The anemia is characterized by a high hemoglobin index, often over 1, with relatively slight morphologic changes in the

[9] Loc. cit.
[10] Thèses de Paris, 1905, p. 135.
[11] Loc. cit.

erythrocytes. It therefore constitutes an additional form of anemia of the hyperchromic type.

3. Edema bears no constant relation to the presence or absence of the anemia.

4. The character of the anemia suggests profound alterations in the activity of the hematopoietic organs.

THE PRESENT STATUS OF THE TREATMENT OF HAY FEVER AND ASTHMA.*

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The observations, statistics and conclusions set forth in this paper are founded on about 2000 case histories of asthma, hay fever and allied conditions treated during the past four years. An attempt has been made to determine, as accurately as possible, such advances in the modern treatment of these conditions as are due to the recent discoveries in the field of allergy, or human hypersensitiveness.

For more than ten years we have been treating hay fever by injections of pollen extract[1] and now have sufficient data to judge whether it is advisable to continue such treatment. At the end of each season a questionnaire is sent to the hay fever patients, which they are requested to fill out and return, checking the class to which they think they belong. Class A means that the hay fever has been entirely relieved, Class B greatly diminished, Class C diminished, but to a slight extent, and Class D, hay fever as bad as ever. The following table shows the number of answers returned each year with the percentage in each class for the last four years:

Year.	Number of answers.	Class A, per cent.	Class B, per cent.	Class C, per cent.	Class D, per cent.
1917	379	20	52	18	10
1918	400	25	51	15	9
1919	473	25	49	17	9
1920	522	20	44	24	12
Total	1744	23	49	18	10

Roughly we may say 25 per cent are entirely relieved, 50 per cent are quite comfortable, 15 per cent are slightly relieved and 10 per cent are not helped. In other words, 75 per cent of the

* Read before the Scranton Medical Society, March 1, 1921.

[1] For full details of such treatment see R. A. Cooke, Medical Clinics of North America, November, 1917, No. 3, 1.

patients can go about their business suffering very little discomfort. This is a great improvement over the time when a patient had but two alternatives—a trip to the White Mountains or Europe during the season of their disability, or else local nasal treatment either by sprays or operation, which nevertheless fails in the majority of cases.

The results of treatment vary somewhat according to the severity of the season, the strength of the extract used and the intelligence of the patient. All of these factors can and will be modified for the better as time goes on. Cities will make provision for the destruction of ragweed before it has a chance to pollenize, patients will learn more of the principles of the treatment and give valuable aid in the graduation of their doses, and finally it now seems as if the greatest difficulty of all, preserving the proper strength of the extract, has been overcome. Heretofore we have been unable to make an extract which would retain its strength for more than two or three months, but within the last year we have obtained one which has kept practically stable for over six months, long enough to last from the beginning of treatment through the season without changing from one extract to another.[2]

At present I do not think we can hold out to our patients the hope of permanent immunity. Occasionally a case is apparently cured by one or more years' treatment, but these cases are prone to relapse, and it is safer to advise treatment each year. Fortunately there is a natural tendency to outgrow the hypersensitiveness, and we have a number of cases on record of spontaneous cure, so that it is well to protect the patient by injections until such a happy result occurs. Even if a case does badly the first year it is well to persevere with the treatment, as there is frequently improvement during the succeeding years. Patients cannot become more sensitive by the injections, and the majority of the failures are due to too small doses or to inability to discover and use the particular pollen to which the case is hypersensitive.

When should we advise operative procedure on the nose? If there is obstruction all the year around, that is manifestly due to a pathologic condition and not to an allergic reaction to something besides pollen (as dust, sachet, chicken epithelium), this can probably be improved by operation, and this will, of itself, lessen the severity of the hayfever; but if the nose is perfectly clear except during the season we have found that operation is not advisable and will be of no benefit to the patient. On general principles, operations should not be performed during the pollen season, as the reaction from the trauma to the already inflamed mucous membrane will greatly increase the discomfort.

[2] Full details of the preparation of such an extract will shortly be published by Dr. Authur F.Coca, of the Department of Bacteriology and Immunology, Division of Immunology, Cornell Medical School.

The disadvantages to the pollen injections are negligible with one exception, and that is the danger of an overdose causing a constitutional reaction. This may occur in from 1 to 2 per cent of all injections and takes the form of a sudden general urticaria or an acute attack of asthma or hayfever. The reaction manifests itself in from five to thirty minutes after the injection and can be promptly controlled by one or more injections of epinephrin (1 to 1000 solution) hypodermically. An initial dose of 6 to 10 minims is used, and this can be repeated in ten minutes if necessary. A third dose is almost never required, and there is no disadvantage in the use of the epinephrin except a nervous, shaky, chilly feeling when more is given than is necessary. This passes off within fifteen to twenty minutes. After a constitutional reaction the next dose of the pollen extract should be decreased slightly and then gradually increased again. With our more stable extract we are working out a system of increases which will practically eliminate the danger of constitutional reactions.

Injections are given every five to seven days, which take but a moment and give very little local reaction except a slight swelling, soreness and itching of the arm. The maximum dose should be reached before the season starts, and should be repeated every five to ten days during the season, as the immunity derived from each injection lasts but a week or so and then rapidly begins to diminish.

We usually employ an extract from a single pollen—timothy for the early cases and ragweed for the late, as the largest percentage of all the trouble comes from these two, either because of their greater prevalence or their greater activity. The cases unrelieved or only partially relieved by a single pollen extract should receive in addition extracts of other pollens to which they are found to be sensitive.

In addition to the pollen injections other measurers are of value in relieving the patient's discomfort. During an acute attack a thorough cleansing of the nose with a dilute solution of adrenalin and cocain will give better drainage and a similar solution in the eyes allays the itching and burning. It is wise to avoid excessive exposure, and if it is necessary to take a long automobile ride through the country on a dusty road it is well to wear goggles to protect the eyes, as much of the pollen is conveyed to the nose by way of the nasal duct. Atropin tablets, $\frac{1}{200}$ to $\frac{1}{150}$ grain, will dry up excessive nasal secretion and relieve slight attacks of asthma. For a severe attack of asthma it is necessary, of course, to give epinephrin hypodermically in 6 to 10 minim doses, repeated as occasion may require. Do not give morphine. Its immediate effect is inferior to the epinephrin, it has unpleasant after-effects and there is always the danger of forming a habit. Patients are often more comfortable if they sleep propped up in bed and with

the windows closed. Ragweed should be eradicated from the immediate neighborhood as far as possible.

Let us now take up the more difficult but fascinating study of asthma. The best definition and classification is that given by Cooke:[3]

Bronchial asthma is a condition characterized by dyspnea, both inspiratory and expiratory, due to edema of the bronchial mucous membrane and possibly to bronchial spasm. It may be acute, subacute or chronic. The term *bronchial asthma* should be restricted to that condition which is the result of an allergic action.

CLASSIFICATION.

1. Allergic	(*a*) By inhalation	Animal dander. Pollens. Sachets and perfumes.
	(*b*) By ingestion.	Drugs. Foods.
	(*c*) By absorption from focus	*Bacterial proteins (very questionable).*
	(*d*) By subcutaneous or intravenous injection	Therapeutic sera.
2. Non-allergic		Acute bronchitis. Chronic bronchitis and emphysema. Pulmonary tuberculosis. Cardiorenal disease. Thymic enlargement. Enlarged bronchial glands. Reflex bronchial spasm.

In diagnosing a case of asthma our chief reliance in finding out the source of the trouble (after a careful history has been taken) is the skin test. This is founded on the discovery that usually the skin of an allergic subject manifests the same hypersensitiveness as the nasal and bronchial mucous membranes, and if an extract of a foreign substance to which the patient is hypersensitive is introduced into the skin a characteristic urticarial wheal will result. There are two common methods now in vogue of performing such skin tests: The intradermal and the dermal or scratch method. In the first a minute quantity ($\frac{1}{100}$ cc) of a fluidextract is injected into the layers of the skin by means of a fine hypodermic needle. In the second the skin is incised with a sharp scalpel, not deeply enough to draw blood; the dry substance is placed on the incision and a drop of $\frac{N}{10}$ sodium hydrate is added to dissolve the substance and bring it into contact with the skin. We have used both methods and find they each have their advantages and disadvantages. The intradermal method is easier to handle, is quicker and more delicate. Its disadvantage is that it is more liable to cause a constitutional reaction, due to the fact that it is

[3] Tice's System of Medicine (in press).

more delicate. While these constitutional reactions are rare they are sufficiently unpleasant when they do occur to demand every safeguard one can employ against them. They are exactly like those caused by an overdose of pollen extract and are controlled by an injection of epinephrin. They occur most frequently when testing with horse serum (in a 1 to 10 dilution), horse epithelium and egg-white. With the scratch method constitutional reactions are less liable to occur, but at the same time one is liable to miss many reactions which are perfectly plain and decisive with the intradermal method.[4]

The accuracy of the skin tests varies according to the substance used. With pollen, animal epithelia and sachet extracts they are extremely accurate in proper dilution. That is, they give corresponding reactions almost invariably at any time they are tried on the same subject, and are almost always indicative of being a causative factor in the patient's trouble.

The food tests are much less reliable, as the following table will show.

	Positive history, positive reaction.	Negative history, negative reaction.	Positive history, negative reaction.	Negative history, positive reaction.	Reaction and history correspond, per cent.	Reaction and history do not correspond, per cent.
Pollen cases . .	155	29	4	4	96	4
Animal epithelia cases	20	17	2	0	95	5
Food extract cases .	9	6	11	3	50	50

Thus with the food reactions we are less certain of our ground. They often give different reactions at different times (and we have not been able to determine that this is due to the patients' having recently eaten or abstained from such food,) and we often find instances in which the skin reaction does not agree with the clinical history at all; that is, patients may eat with impunity foods giving positive skin reactions or may have very definite trouble from foods giving a negative reaction. It is easy to see why this should be so. Pollens, animal epithelia and other inhalants come unchanged in direct contact with the hypersensitive mucous membrane and produce their effects almost at once. Foods introduced into the gastro-intestinal canal are broken down into other split products, then absorbed and brought into contact with the hypersensitive membranes in a quite different form from the original food and may produce their effects hours or days after their ingestion. Eventually we will know more of these split products and their delayed or negative reactions will then be explained.

Skin reactions to milk and eggs occurring in children hypersensitive to such foods seem to be more reliable than other food test in adults. This hypersensitiveness they almost invariably

[4] Dr. Aaron Brown, in a paper to be published shortly, will give in detail the experiments on which these conclusions are founded.

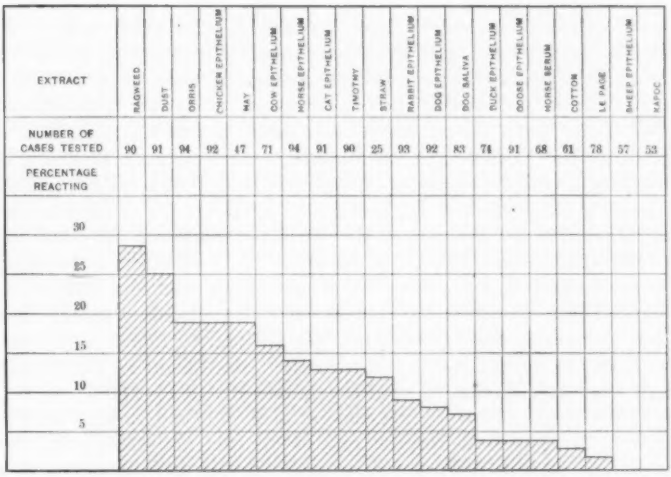
outgrow in later life. We are convinced that the role of foods as a causative factor in the production of asthma has been greatly overestimated in the past, and that the great majority of cases are due to some inhalant. This conviction is based on the fact that it is usually impossible to induce an attack of asthma by the ingestion of foods giving positive reactions, that patients are often free of asthma for long periods of time while still eating such foods, and conversely often continue to have asthma even though obstaining from such foods.

The following table will give an idea of the relative frequency of the various causes of asthma, comparing 135 cases treated in 1917 and 122 cases treated in the first six months of 1920. This table excludes patients seen only once or twice and comprises those in whom it was felt a diagnosis should have been made. They are listed under what was determined to be the actual cause of the asthma and do not take into account positive skin reactions to substances to which the patient was not exposed—that is, if a patient gave positive skin reactions to ragweed and dog epithelium, but did not come in contact with dogs and only had asthma in the autumn with hayfever, he is listed as a pollen asthma and not as a mixed asthma. Thus the figures for "mixed" asthmas do not represent the actual number of cases of multiple hypersensitiveness, which would be considerably higher than those given in the table.

Year.	Number of cases.	Pollen, per cent.	Undiagnosed, per cent.	Mixed, per cent.	Animal, per cent.	Bacterial (questionable), per cent.	Food, per cent.	Dust.
1917	135	38.5	29	14	9	8	1.5	0
1920 (6 mos.)	122	24.0	17	38	5	10	2.0	4

A study of this table reveals several interesting points: (1) Our undiagnosed cases are decreasing as our knowledge increases; (2) the mixed cases increase at the expense of the pure pollen and animal cases; (3) the food and bacterial cases remain about the same and are a small percentage of the whole; (4) we have discovered a new and very important class of exciting agents, the dusts, which, while they affect a very small number of people as a pure group, account for most of the increase in the mixed class.

The preceding table gives the percentage of the different classes of asthma, but it is of interest to know something of the relative frequency of sensitiveness to the most common substances. A study was made of 100 consecutive cases of hypersensitiveness, excluding uncomplicated hay fever, and the results are give in the following table. All cases were not tested with every substance, but where less than twenty tests were made with any single extract it was excluded from consideration in the table:



A study of the chart shows that ragweed and dust most frequently gave positive reactions, the former being twice as common as timothy. Chicken epithelium and orris were also common. Hypersensitiveness to horse epithelium was nearly five times as frequent as to horse serum.

Similar tables have been made for the various foods, but it is felt they are of little value because of the unreliability of the food skin reactions as referred to above.

Having made our diagnosis by the aid of the history and cutaneous reaction, what can we do in the way of treatment? First, we must learn to discard the word "cure." Once an asthmatic a patient is usually a potential asthmatic for the rest of his life, just as a diabetic is potentially a diabetic whether his urine is sugar-free or not. Many do outgrow their hypersentiveness as we all know, but it pays to take no unnecessary chances in waiting for this occasional happy result to occur. The one rule to follow is, "Remove from the environment of the patient all causative factors that can be removed and immunize him against all those that cannot be otherwise controlled." For example, we find a patient hypersensitive to ragweed, cat epithelium, chicken epithelium and several foods. We advise him to allow no cats in his house, substitute silk floss or cotton pillows for his feather ones, have several thorough house-cleanings to remove all the feather dust already present in his house dust; omit the particular foods from his diet, and then immunize him with ragweed pollen injections during the season. If we omit any one of these procedures (except possibly the diet) he will probably continue to have his asthma as before; and if, in spite of all these procedures, he continues to

have asthma it means we have overlooked some other cause. In at least 80 per cent of all cases we can get skin reactions to one or more extracts, and in a large percentage of these a satisfactory result can be obtained if the patient is willing to follow directions. This latter point is important, and much depends on the intelligence of the patient. When in spite of demonstrable evidence in the way of skin reactions he refuses to believe that a feather pillow, which he has treasured for years, may be the cause of his trouble, or insists that the presence of the cat in the house can have nothing to do with his discomfort, as he never picks it up, it is hopeless to try to benefit him. But if he once grasps the idea (and with marked skin reactions it is usually easy to persuade a person that that particular substance is not a good one to allow in contact with his bronchial mucous membrane), the battle is more than half won, and one has secured a valuable ally in his fight.

If the result is not at first successful it does not mean that the patient faces asthma for the rest of his life, and this should be explained to him. We are constantly finding new causes, and a case which resists treatment now may yield very readily and simply six months from now, when our knowledge is greater. During the past year we have made a great advance in solving many of our so-called "dust cases." In 1917, we found that many of our cases gave marked skin reactions to extracts of dust collected from their houses (preferably with a vacuum cleaner). These reactions are not necessarily individual—that is, if a patient reacts to one dust he may (and usually does) react to several or all, although occasionally we find a case reacting to his own dust and no other. It is difficult to find out the exact ingredients of dust, but it is probably chiefly made up of feather dust, orris and insecticide powders, stuffing of mattresses and upholstered furniture, animal emanations from household pets and from rabbit hair, commonly used as filling for sofa pillows and cushions. Extracts can be made from each separate pillow, mattress, couch stuffing, etc., and the patient tested with these often gives positive reactions from one or two and negative from the rest. The articles giving positive reactions are then removed from the house, and after a thorough house-cleaning the whole dust is again tested; if it is negative we can be sure that the cause of the trouble, in that direction at least, has been removed.

The whole procedure, unfortunately, is not as simple and satisfactory as these few words would seem to indicate. All too often the feather pillows are removed from the bedroom, a thorough house-cleaning is done and the patient is well and happy for five or six weeks, only to come back at the end of that time with a return of the asthma. In many of these cases the explanation lies in the gradual filtering in of the dust from other rooms where feather pillows still abide and a gradual loss in zeal of the house-

cleaner. It is easier to accomplish results in the homes of the well-to-do, where the rooms can be better isolated and where the patient and his family are intelligent in their coöperation. Unfortunately many of our clinic cases come from the tenements, where six or eight people live in four or five closely connected rooms, speak our language imperfectly and have not the vaguest idea what all the commotion is about. They want a good asthma medicine to take internally. In the clinic which we have been conducting at the New York Hospital for the last year this difficulty showed itself at the start and our results were discouraging. We solved part of the problem by the aid of a visiting nurse who went to the homes, collected samples of dust, saw that our recommendations were being carried out and had a chance to explain more fully our object. Results improved but still left much to to be desired, and now we are trying to supplement our work by making up extracts from the dusts from the various homes, and, if they give good skin reactions, using them for active immunization as we do pollen extracts. This is, of course, in conjunction with the removal of any definite exciting cause and thorough house-cleaning. Since then we have been able to see a marked improvement in our results, but it is still too early to say how much we can accomplish. This much can be vouched for, that the idea is gradually spreading among our patients that dust in a home is not lucky for an asthmatic and that silk floss or cotton pillows are often better than those made of feathers or rabbit hair. One patient who improves teaches the others, and in time I hope the new conception of asthma will be as well known among the laity as the cause and prevention of tuberculosis now is.

So far nothing has been said about bacterial extracts and bacterial vaccines over which so much enthusiasm has been raised in the last few years. Sicard[5] published in 1917 a series of cases of bronchial asthma treated by vaccination with apparently satisfactory results. In 1919 Walker[6] reported on the treatment of asthma by bacterial vaccines and bacterial extracts. He divided his groups into those that gave positive cutaneous reactions to bacterial proteins (7 per cent in a series of 400), and those treated with bacterial extracts or vaccines that had shown no positive cutaneous reaction to any substance with which they were tested. In the first group, those that were sensitive to bacterial proteins, treatment was carried out by the injection of vaccines of the same bacteria, and the author records 75 per cent of the patients of this group as having been relieved of their asthma. Of the non-sensitive patients treated with bacterial vaccines only 37.5 per cent were relieved of asthma and 25 per cent were markedly improved.

[5] Treatment of Bronchial Asthma by Vaccination, with report of Cases, Am. Jour. Med. Sc., 1917, **158**, 856.

[6] Treatment of Bronchial Asthma with Vaccines, Arch. Int. Med., 1919, **23**, 220.

Later, Rackeman[7] published the results of his observations on 39 patients, and concludes that the treatment was successful in fairly close accordance with the presence of a positive skin test.

Our own experience with bacterial extracts and bacterial vaccines has been so unsatisfactory and so out of accord with the figures given above that it seems necessary to subject the whole question to a more careful and critical review.

Karl F. Meyer[8] has shown that cutaneous hypersensitiveness to bacterial proteins is only induced by an active infection. Further, he has shown that this hypersensitiveness is only temporary. If the treatment of asthma is specific it should be possible to demonstrate the presence of that particular organism, in the sputum or elsewhere, to the protein of which the case shows a cutaneous reaction. This, however, has not been possible, as stated by Walker and amply substantiated in our own cases.

In addition, if a bacterial protein giving a positive cutaneous reaction is in fact the real cause of the asthmatic manifestation in any individual, then the injection of such protein subcutaneously in sufficient amounts should produce a constitutional reaction manifested by an acute attack, as can be done so readily with the epithelial and pollen extracts. In spite of many attempts no such result has yet been obtained.

Another test of the hypothesis that bacterial proteins are themselves causes of asthma would be the therapeutic efficiency of bacterial vaccines or extracts. In our own cases treated in this way, satisfactory results are not obtained in more than 10 per cent of the cases, and this is such a small percentage that the apparent improvement can readily be attributed to unknown factors.

It is a great mistake to consider bacterial infections as true etiologic factors for hypersensitiveness in the sense in which that term is used today. Cases of asthma that cannot be diagnosed by cutaneous tests with pollens, animal emanations, sachet powders, drugs or foods have conveniently been considered as examples of the bacterial reactions. A study of our records of five years ago shows that we were diagnosing but 50 per cent of the cases, whereas today we are able to diagnose 73 per cent, not counting the so-called bacterial group. This improvement has all been at the expense of the so-called bacterial cases.

All of which shows that the more carefully this subject is studied the greater is the percentage of those that can be definitely diagnosed without any regard for the hypothetical bacterial hypersensitiveness. I do not wish to be understood as saying that bronchial infection does not occur, for of course it does; and we must remember that secondary infections occur wherever con-

[7] The Relation of Sputum Bacteria to Asthma, Jour. Immun., July, 1920, No. 4, **5**.
[8] A Résumé of Some Experimental Studies on Cutaneous Hypersensitiveness, Am. Jour. Dis. of Children, December, 1919, **18**, 577–590.

gested and edematous mucous membrane exists. In some cases of secondary bronchial infection of long standing, autogenous vaccines given in gradually increasing doses over a period of time may bring about definite improvement as far as the infection itself is concerned, but it will not affect the asthmatic manifestation. Needless to say, manifest pathologic conditions of the nose and throat, such as polypi, deviation of the septum, hypertrophy of the turbinate bones or infected tonsils, must be appropriately treated surgically. But it must also be borne in mind that polypi may be the sign of a chronically edematous, hypersensitive mucous membrane rather than an infected sinus, and that removal of the specific factor will go a long way toward clearing up the associated infection.

I have spoken at length as to treatment by removal of the cause. Now for a few words as to treatment where the cause cannot be removed. This is usually the case with pollen asthmas, for while some of them can get away during the season, many cannot, and in any event it is a real hardship to be obliged to leave one's home when it may be not convenient. Pollen asthma is treated precisely as the associated hay fever by pollen extract injections with about 80 per cent satisfactorily relieved, a better record than that of the associated hay fever. The injections not only relieve the asthma but minimize the danger of subsequent bacterial infection and the production of a chronic bronchitis or sinusitis. They also lessen the danger of a rhinitis and bronchitis during the succeeding winter. It is occasionally necessary to immunize against horse, dog or cat epithelium, and this too can be done very successfully, but it must be remembered that the immunity is not permanent, and it is necessary to give injections once a month or so to maintain it. I have already spoken of giving injections of autogenous dust, and this has been a great help in controlling our dust asthmas, particularly in our clinic cases.

In children hypersensitive to milk, eggs or wheat it is often a difficult problem to decide what to do. If they are hypersensitive to but one of the three it is better not to try immunization but to omit that article of food from their diet until they naturally outgrow their hypersensitiveness. Where all three are involved it is difficult to make up a nourishing diet without them. Often they can take goat's milk instead of cow's milk. It is possible to immunize them against any one of the three by injections of the protein or by feeding minute quantities by mouth, but it is a difficult, tedious process and often unsuccessful. Park[9] reports a case of immunization to cow's milk where an initial dose of one drop, well diluted, gave a marked constitutional reaction.

Results of treatment of asthma are more difficult definitely to

[9] A Case of Hypersensitiveness to Cow's Milk, Am. Jour. Dis. of Children, January, 1920, **19**, 46–54.

determine than those of hay fever. The latter is limited to a certain time of the year, and at the end of the season it is possible to get a fairly accurate estimate of the condition during exposure. With most of the asthma cases, except those due to pollen, it is an all-year-long affair, and it is difficult to follow the patients indefinitely. They may not report because they are entirely well and do not think it necessary; or because they are fairly well and too busy to bother about it; or because they are just as bad as ever and disheartened at their failure to find relief. A careful study of the 122 cases cited under the first six months of 1920 has shown that from the histories and questionnaires sent out we have data enough on 67 patients (excluding the 17 per cent undiagnosed) to make a fairly accurate estimate of their results six months to a year after treatment. Using the same classification as with hayfever we find 40 per cent in Class A, 35 per cent in Class B, 15 per cent in Class C and 10 per cent in Class D. This is not put forward as an accurate statement of the end-result of the treatment of all asthma cases, as the number is entirely too small, but is merely an indication that probably 75 per cent of all asthma cases, where a diagnosis can be made, can be brought to a state of comparative comfort. Those cases due to animal epithelia do best, with the pollen, food, mixed and bacterial asthmas following in the order named.

Conclusion: In conclusion, I wish to cite the history of a typical "dust case," illustrating the difficulties encountered in such cases and the eventual success obtained with careful management and treatment.

The patient was a woman, single, clerk, aged twenty-eight years. She had had asthma since five years of age, almost continuously for the past few years, and with acute exacerbations which kept her from working. She had had several nose and throat operations without relief. Skin tests were positive for ragweed, chicken feathers and orris. The attack which brought her under our observation, lasting six weeks, coincided with the gift from a friend of a box of highly scented talcum powder. She lived in a single room in a girls' dormitory with eight other girls on the same floor. She moved into a new room which had been carefully cleaned and was without feather pillows or talcum powder. Her asthma promptly cleared up and she stayed well for three months, going to work every day. She then began to have a little asthma and further tests were made which showed, among other things, a hypersensitiveness to rice powder. This was an ingredient of a new face powder she had just begun to use and its removal promptly cleared up the asthma. She was then well for six weeks until she went home for a visit. Her case had been explained to her family, but they did not believe in such nonsense, and no effort was made to clear her room of feathers until she arrived, when she

removed the pillows herself. After one night there she developed asthma, which cleared up on her return to New York. In September she took a trip to Pennsylvania during the height of the ragweed season, and although she had been receiving ragweed injections and was perfectly comfortable in New York, the doses evidently had not been sufficient and she developed asthma during a dusty automobile ride. This cleared up on returning to New York and she remained well for two months, when severe asthma returned and no cause could be found to account for it. It then occurred to us that her room might have become saturated again with dust from the rooms of the other girls on the same corridor, as it was swept out into the hall and past her door without any special effort being made to keep it out. An extract was made from dust collected from a small rug near her bed which had not been beaten for a long time, and this gave a marked positive skin reaction. Her room was again carefully cleaned, the rug beaten every few days, the door closed while the corridor was being swept and she was given injections of her own dust extract. Her asthma gradually cleared up and she has been practically free for eight months, with the exception of a few slight attacks which have not prevented her from working.

To some this may not seem like a particularly brilliant result, as she has had three or four attacks of asthma during the past year; but they have all been short ones and she has been able to work practically all the time instead of being confined to bed for a week or two every month. She is intelligent and anxious to help herself, and knowing her various hypersusceptibilities she will be more able to avoid the causes of them in the future. The less asthma she has the less she is likely to have, and she may in time entirely outgrow her hypersensitiveness.

SYPHILITIC BACKACHE.

By Warren Thompson, M.D.,
OMAHA, NEB.

Backache presents one of the common and frequently one of the most difficult problems arising in the course of a day's work. Among the many causes for this complaint, syphilis has received but little attention. Two cases which presented themselves with a chief complaint of backache, in whom syphilis of the spine was diagnosed, seemed sufficiently interesting and instructive to warrant a report and a brief review of this condition:

Case I.—Mrs. V. A., aged fifty-nine years, 1916, housewife. Two children living and in good health. There have been no miscarriages.

Past Illness. She stated that she had always enjoyed good health until the onset of the present trouble.

Present Illness. The patient was admitted with a chief complaint of backache, affecting the lower dorsal and lumbar regions. The trouble began five years ago with a dull ache, which came on after a hard day's work. Rest always relieved it at that time. Last winter the "bad back" began to trouble again and the pain was described as "pulling like." The attacks were repeated every few weeks, but were always relieved by rest. Four months ago the back trouble became more constant and lying down gave no relief. The pain was dull and was described as "though the muscles were all drawn up in the lower part of the back." The backache was particularly troublesome at night. Pressure over the aching parts increased the pain. The patient had been confined to bed for the past seven weeks on account of the pain. The pain bore no relation to urination, defecation or menstruation—in fact the menopause had come on eight years previously. Weather changes did not influence the backache.

Physical Examination. The patient was a poorly nourished, sallow woman. The teeth had all been extracted. The tonsils were buried. The cornea of the right eye was hazy and the patient stated that it had been so since a girl of thirteen. The pupils were irregular and reacted sluggishly to light. There was a slight systolic whiff at the apex and a somewhat accentuated second sound at the base. Nothing noteworthy was found in the examination of the lungs or abdomen. The back was rigid from the tenth dorsal vertebra on down. Percussion over the lower dorsal and lumbar vertebræ caused pain. No tumor masses could be palpated along the spine. There was a slight curvature to the left. Attempted motion was restricted in all directions and produced pain.

The pelvic examination was negative.

The urine, stomach contents and stool examinations were negative. The blood Wassermann was three plus positive. On account of the fixation of the spine a spinal tap was not attempted. Radiograms showed a thickening of the periosteum with some bony deposits at the tenth, eleventh and twelfth dorsal vertebræ.

Vigorous antiluetic treatment was instituted and the backache gradually subsided after four weeks in the hospital.

Although the patient neglected to return for further observation, serologic tests and treatment, in answer to a recent communication she reports that she has been entirely free from backache since her departure from the hospital.

Case II.—Mr. I. A., aged thirty-eight years, farmer, consulted me for backache October 21, 1916. One child living and in good health.

Past Illness. Negative. The patient denied venereal infection.

Present Complaint. The chief complaint was backache, affecting the left side of the spine at the level of the tenth dorsal to the first lumbar vertebra. He has not noticed any local tenderness. Bending or stooping did not increase the pain. He stated that it was somewhat worse after lying down. The weather at times seemed to affect the pain, it being worse in damp, cold weather and easier during warm weather. Last year the patient had what he called "sciatica" in the left leg. His backache was always worse at night.

Physical Examination. A poorly nourished, sallow man, who appeared older than his stated age. The teeth were in good condition and the roentgen-ray films were negative. The tonsils appeared normal, there being no injection of the pillars and no palpable cervical glands. The pupils reacted slowly to light and normally to accommodation. The left pupil was irregular. The right abdominal reflex was not so marked as the left, the lower right being nearly absent. The knee-jerks, ankle-jerks and other reflexes were normal. There were no sensory changes.

There was some fixation of the lower dorsal and lumbar vertebræ. Percussion over this area produced excruciating pain, especially on the left side at the level of the first lumbar vertebra. Motion was somewhat limited but did not increase the pain materially. No tumor masses were palpable.

The right tibia was very rough and tender to palpation and to percussion.

Nothing noteworthy was found in the examination of the heart, lungs and abdomen.

The urine examination was negative.

The blood Wassermann was four plus positive. The spinal fluid showed increase in globulin, cell count 16 and Wassermann four plus.

Radiograms of the spine were negative.

The patient was put under antileutic treatment and the relief from the backache was complete. Likewise the spinal fluid and blood Wassermann were negative.

There was no return of the backache until February, 1921. Physical findings at the time were practically the same as at the time of the original examination. The spinal fluid showed a cell count of 4. The globulin, colloidal-gold and Wassermann tests were negative. The blood Wassermann was four plus positive. A roentgen-ray plate of the spine was negative. The backache has again entirely disappeared after antiluetic treatment.

Remarks. The occurrence of syphilis elsewhere in bone tissue has been frequently recognized and is not particularly uncommon. Syphilis of the vertebral column, however, although rather a rare condition, is probably frequently overlooked. Whitney[1] in the

[1] Syphilis of the Spine: Its Frequency and the Value of its Characteristic Lesions as a Diagnostic Sign in Syphilis, Jour. Am. Med. Assn., 1916, **66**, 627.

examination of 544 syphilitics studied at the University of California Hospital, diagnosed syphilitic joint disease in 83, or 15.2 per cent, and of this number 41 showed involvement of the spine. Although syphilis may affect any part of the spine the most frequent sites are the cervical and lumbar regions, over one-half the reported cases affecting the cervical vertebræ. Hunt[2] gives the following figures in 88 cases collected by Ziesche: Cervical cases, 61; dorsal cases, 12; lumbar cases, 5; sacral cases, 2; cervical and dorsal, 1; dorsolumbar, 3; diffuse, 4. Age does not seem to be a factor, as it has occurred in cases of hereditary lues as early as four years and as late as sixty in acquired cases. It usually is a tertiary manifestation; however, it has been suggested that the backache so common during the secondaries may possibly be due to a mild periostitis occurring at that time. Trauma is a probable factor and may explain the high percentage of cervical cases. In cervical cases the frequent association of pharyngeal ulcers and gummata has been noted and the possibility of direct extension to the spine has been suggested (Hunt).[3]

Symptoms.—Pain is usually the chief symptom. It may come on suddenly, similar to that produced by an acute focal infection, or the onset may be gradual, extending over a prolonged period of time, manifesting itself by a general soreness. It is generally definitely localized in the part of the spine involved unless there is an associated involvement of the posterior nerve roots or the cord itself, in which cases the distribution or radiation of the pain varies accordingly. One very characteristic and diagnostic feature lies in the fact that the pain, although quite constant, is invariably greatly intensified at night. (This information was volunteered by both cases herein reported.) Local tenderness is marked, which becomes acute on percussion over the affected area. There is limitation of motion and attempted movements of the spine show increased rigidity and aggravate the pain. Whitney states: "The characteristic thing is not the hypertonicity alone, but this combined with a stiff back or with a back showing areas of restricted mobility. This combination of two findings we have regarded as almost sure proof of syphilis, and it is one of the points we especially desire to emphasize in this paper, that in this we have a pathognomonic sign which is of quite as much interest to the general diagnostician as to the orthopedist." If the bony involvement is extensive slight swelling or considerable tumefaction is visible. Attention has been called particularly by Sachs,[4] Hunt[5] and Wholey[6] to the bizarre

[2] Syphilis of the Vertebral Column: Its Symptomatology and Neural Complications, Am. Jour. Med. Sci., 1914, **147**, 164.

[3] Loc. cit.

[4] Specific Vertebral Osteitis Simulating Specific Pachymeningitis. Section on Neurology and Psychiatry, New York Academy of Medicine, January, 1913.

[5] Loc. cit.

[6] Complicated Nerve Tissue Involvement Arising from Syphilis of the Vertebræ, Jour. Am. Med. Assn., 1916, **66**, 627.

nervous symptomatology which may arise, presenting no characteristic picture but depending on the location and extent of the nervous involvement. Wholey[7] remarks: "Frequently it is through some manifestation in the widely varying symptomatology arising from nervous involvement that the existence of osseous disease is suggested rather than through any symptoms arising directly from the spondylitis."

Pathology.—The pathology is similar to bone syphilis elsewhere. It may be a simple periostitis, an osteitis or a combination of both, depending on the extent of the process. Syphilis tends to form new bone, and the nodules which thus arise frequently make pressure on nerve roots, thereby acting mechanically as a factor in the production of pain. Gummatous formation in the body of the bone may undergo liquefaction necrosis. Charcot's joints may involve the spine, and although still a moot question as to whether such joints are truly syphilitic or parasyphilitic, similar symptomatology may arise. Kerr[8] states that only 2 cases of Charcot's joint involving the spine were recorded out of 300,000 cases seen in the outpatient department of the Massachusetts General Hospital in three years. Whitney[9] calls particular attention to a synovitis, the synovia of the various spinal joints being attacked, "Leading at first to lessened motion from spasm, but as the acuteness of the process subsides, adhesions are usually formed which limit motion and in many cases give complete fixation." Roberts[10] states that "There is sufficient evidence that backache may in some instances be due to a myositis caused by syphilis toxins to warrant further investigation of this subject." The nervous pathology is a result of the compression of the spinal cord and nerve roots incident to the spondylitis. If the disease is extensive a compression myelitis may develop at the level of the bony involvement. Spontaneous fracture may be an end-result, particularly in the Charcot joints (Kerr).[11]

Diagnosis. The diagnosis of syphilitic backache necessitates the careful exclusion of all other possible factors producing backache. The various causes in the production of backache are too numerous to justify any attempt at a detailed differential diagnosis in this paper. Special attention, however, should be called to several conditions with which it is particularly liable to be confused, namely, osteoarthritis from focal infection, tuberculosis, metastatic invasion of the spine from malignant tumors and typhoid spine.

Infective arthritis usually involves many vertebræ, whereas syphilitic spondylitis is characterized by the limited number of

[7] Loc. cit.

[8] Report of Three Cases of Syphilis of the Spine and Three Cases of Spontaneous Fracture, Jour. Nerv. and Ment. Dis., 1916, **44**, 346.

[9] Loc. cit.

[10] Syphilis as a Cause of Backache, New York State Jour. Med., 1919, **19**, 20–24.

[11] Loc. cit.

vertebræ involved. In Ziesche's series, quoted by Hunt,[12] the following figures are significant as to the number of vertebræ involved: 1 vertebra in 25 cases, 2 vertebræ in 17 cases, 3 vertebræ in 11 cases, 4 vertebræ in 3 cases, diffuse in 4 cases.

Tuberculosis is particularly liable to be confused. Sloan[13] states that in a series of 70 cases of supposedly tuberculous spondylitis cases in the Foundling Hospital in London, 7 per cent showed positive Wassermann reactions and cleared up under antiluetic treatment. Roberts,[14] in his remarks on syphilis as a cause of backache, states that probably 50 per cent or more of the conditions which we have heretofore ascribed to tuberculosis are really of luetic origin. Roentgen-ray findings and evidence of tuberculosis elsewhere in the body are helpful in differentiating these conditions.

Typhoid spine must be considered but is usually readily differentiated by roentgen-ray evidence and the history of a previous typhoid infection.

Metastatic invasion of the spine demands a careful search for a primary malignancy, and this, combined with rather definite roentgenologic findings, makes for a positive diagnosis.

The roentgen-ray is a valuable aid, and yet in early lesions the findings are often negative. Periostitis is manifested by a diffuse thickening of the periosteum with possibly some bony deposits. New-bone formation is a characteristic of syphilis involving the bone. Gummata involving the body of the spine with little evidence of new-bone formation are particularly confusing, the differentiation of this condition from tuberculosis or metastasis from malignant tumors being difficult. In more advanced cases of syphilitic spondylitis the picture is so definite that the roentgenologist can make the diagnosis unaided.

The Wassermann Test. The Wassermann, when positive, is a valuable adjunct in diagnosing syphilis affecting any part of the body. It must be remembered, however, that the Wassermann test is frequently negative in syphilis of bone. An exact explanation of this fact is wanting, but Sloan[15] suggests that the rather poor blood supply to bones might account for the smaller percentage of positive reactions in bone syphilis than in syphilis involving the soft tissues. Examination of the spinal fluid should be made whenever the fluid is obtainable, as it is now an established fact that a blood Wassermann in certain cases is often negative when the spinal fluid Wassermann is sharply positive.

A careful search for evidence of syphilis elsewhere in the body is of the utmost importance. Irregular pupils or other manifestations of central nervous system involvement are helpful in arriving at a final diagnosis.

[12] Loc. cit.
[13] Syphilis of the Spine, Cleveland Med. Jour., 1914, **12**, 30–5.
[14] Loc. cit.
[15] Loc. cit.

Therapeutic Test.—The remarkable response of bony syphilis to antiluetic treatment holds true in syphilis of the spine. The bony deposits if present readily disappear and the pain, if due to the spondylitis alone, rapidly subsides.

Prognosis.—Insofar as the backache resulting from syphilitic spondylitis is concerned the prognosis is excellent, particularly in early cases properly treated. The chief concern rests in the nerve and cord involvement, the outcome of which is always uncertain.

Treatment.—The principles in treatment of syphilis apply here as elsewhere. Cases should be controlled with subsequent Wassermanns and roentgen-ray plates. Patients with extensive destruction of the spinal column demand the coöperation of the orthopedist.

Summary.—1. Backache as a chief complaint may be due to syphilitic spondylitis, and although the condition is rare it should be considered as a possibility in every indefinite case of backache.

2. Syphilis may involve any part of the spine; the most frequent location, according to the literature, is in the cervical vertebræ.

3. The pathology is similar to syphilis of bone elsewhere in the body. The nervous manifestations depend on the part of the vertebral column involved and the extent of the morbid process.

4. Syphilitic spondylitis presents no definite clinical picture, the diagnosis being made chiefly by (1) the roentgen-ray, (2) evidence of syphilis elsewhere in the body, (3) the Wassermann test, and (4) the therapeutic test.

THE INCIDENCE OF CECAL TUBERCULOSIS WITH PULMONARY TUBERCULOSIS.*

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AND

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The subject of tuberculosis is particularly interesting to the gastro-enterologist, as digestive symptoms are so frequently the first manifestation of early lung involvement. Then throughout the entire course of the disease a good gastro-intestinal tract is almost a *sine qua non* for recovery. To build up the body resistance an abundance of good, nourishing food must be digested and assimilated. If a tuberculosis patient who has been progressing favorably so far as his pulmonary condition is concerned, reaches a period of standstill or begins to lose ground, there is likely, especially if associated

* Read at the Annual Meeting of the American Gastro-enterological Society, at Boston, Mass., June 6, 1921.

with gastro-intestinal symptoms, to be an involvement of the alimentary tract. These symptoms are anorexia, slight bloating, belching, intestinal discomfort or pain usually localized in the mid or lower abdomen. The pains are crampy in character, suggesting gas pains, and come on at irregular intervals, and are likely to be aggravated by eating. There may be fever not due to the lung condition; also, alternating diarrhea and constipation.

Tuberculous colitis is by no means an infrequent complication of pulmonary tuberculosis. Pathologists tell us that from 70 to 90 per cent of all tuberculous patients show involvement of the gastro-intestinal tract, and Albrecht[1] states that with cavity formation practically all do. It is interesting to note that even Hippocrates[2] recognized the seriousness of diarrhea in consumption, for he says in his aphorisms that diarrhea attacking a person with phthisis is a mortal symptom. The site of the ulcerative lesion, as found by Fenwick and Dodwell[3] in 500 autopsies was as follows: Ileocecal region, 85 per cent (confined to this region alone, 10 per cent); jejunum, 28 per cent; duodenum, 3.4 per cent; ascending colon, 51.4 per cent; descending colon, 21 per cent. The cecum is probably the part first involved and the process extends in both directions. As to the method of infection, it may be either direct from swallowed sputum or the bacilli may be carried by the mesenteric vessels.

Ileocecal tuberculosis in its early stages, at least, is difficult to diagnose by the ordinary clinical methods: Neither the symptomatology, physical examination nor the ordinary laboratory findings give the necessary information. The history points to gastro-intestinal tract involvement, but does not differ materially from that of other conditions, like chronic appendicitis and the non-tuberculous forms of colitis. Alternating constipation and diarrhea, while suggestive, are not always present. Physical examination elicits sensitiveness in the cecal region, and frequently, especially late in the disease, a thickening or tumor can be palpated. Likewise the laboratory findings are of little value. The presence of tubercle bacilli in the feces does not establish the diagnosis, as it has been shown that they exist in the gastric and intestinal contents of patients with pulmonary tuberculosis without any intestinal involvement. Given, then, a patient with pulmonary tuberculosis exhibiting gastro-intestinal symptoms associated with some pain and thickening in the ileocecal region the evidence is favorable to the diagnosis of intestinal tuberculosis. If alternating diarrhea and constipation are also present the diagnosis is almost certain. But to wait until the fully developed symptom-

[1] Frankf. Z. f. P., 1907, 1.

[2] The Genuine Works of Hippocrates, translated by Francis Adams, William Wood & Co., Aphorisms 14, Section V, p. 236.

[3] Lancet, July 16, 1892.

complex is present before making a diagnosis is like refusing to diagnose cancer of the stomach until lactic acid and Boas-Oppler bacilli are found in the gastric contents and a palpable tumor is present. The early diagnosis of the former is just as important as the latter.

Stierlin,[4] of Basle, was the first to call attention to the roentgen diagnosis of ileocecal tuberculosis. In 1911, he reported 6 cases—4 of tuberculous colitis, 1 of cancer and 1 of ulcerative colitis—in which he was unable to fill the cecum and descending colon with the opaque meal. All of the cases were operated upon and the roentgen findings verified. He says in the main: "In infiltrating and ulcerative involvement of the cecum and ascending colon there is an absence of the normal shadow of this part of the colon, as shown in the skiagram six or seven hours after the barium meal, while the terminal ileum and transverse colon are filled. Consequently the early as well as the later stages of the so-called cecal tuberculosis can be diagnosed by this means, even in cases undiagnosable by the ordinary clinical methods."

In 1912, Case,[5] in a paper discussing tuberculosis of the ileocecal region, says: "Ileocecal tuberculosis is a condition which in a certain number of cases can be almost surely diagnosed by the roentgen-ray examination."

In 1917, Pirie,[6] of Montreal, at the request of Dr. Archibald,[7] made some roentgen-ray studies of intestinal tuberculosis. His report is worth quoting:

"Dr. Archibald has asked me if I could write from memory a summary of my findings in tuberculosis conditions of the intestines. I do so with pleasure, as it was about the most interesting work I did for about a year before the war began. Writing as I do without notes from a base hospital in France, I well remember the disappointment we had, as in several successive cases of tuberculous cecum I failed absolutely to help in the diagnosis. Some bad luck seemed to dog my steps, for whereas we had formerly been able to show by means of a barium meal the position, shape and size of the normal cecum, yet we failed, in these tuberculous cases, to catch the cecum at the proper time when it was filled by the meal. Finally the cause of our failure struck us. We could not show the cecum filled by a barium meal because it never did fill when tuberculous ulceration existed. Setting out with this as a working hypothesis we examined the cases at half-hour intervals from four to twelve hours after the barium meal. We found our theory correct in each case of tuberculous cecum, namely, the

[4] München. med. Wchnschr., 1911, **58**, 1231.

[5] X-ray Studies of the Ileocecal Region and the Appendix, Am. Quart. Roentgenol., 1912.

[6] See Archibald's Article.

[7] The Role of Surgery in the Treatment of Intestinal Tuberculosis, Am. Rev. Tuberc., October, 1917, p. 449.

cecum never filled up with the meal. Each small squirt of barium that left the ileum was quickly passed on past the cecum and collected elsewhere in the large colon, either in the transverse or the descending part. So that our conclusion was that in a tuberculous subject with symptoms suggesting tuberculous cecum, if the cecum did not fill from four to twelve hours after the barium meal when examined at intervals of about half an hour, then this want of filling confirmed the diagnosis. On the other hand when it did fill, as it does in a normal individual, it negatived the diagnosis of tuberculous cecum. We had this latter experience confirmed in one case where a clinical diagnosis of tuberculous cecum

FIG. 1.—Barium enema. Normal colon. Complete filling of cecum at "A"

had been suggeted: The roentgen ray showed a cecum filled by barium, and at operation a non-tuberculous cecum was found."

It was not, however, un il 1919, when Lawrason Brown[8] and Homer Sampson, of the Trudeau Sanitarium, published their work on the *Early Diagnosis of Ulcerative Tuberculous Colitis*, that this subject received the attention it deserved. They observed a large number of cases and confirmed *in toto* the work of Stierlin and Pirie. Of their 175 cases of pulmonary tuberculosis examined, 44 were positive, and of these, 28 were operated upon and 27 found

[8] Early Roentgen Diagnosis of Ulcerative Tuberculous Colitis, Am. Jour. Roentgenol., 1919, **6**, 625. Early Roentgen Diagnosis of Ulcerative Tuberculous Colitis, Jour. Am. Med. Assn., July 12, 1919, p. 77.

to be correctly diagnosed. Since then Carmen,[9] from the Mayo Clinic, and others have added to the literature of this subject. The severity of the lung involvement does not necessarily correspond with that of the intestine. The former may be very slight, even arrested, while the latter may be extensive and active.

Pässler,[10] in 1911, reported 2 cases of extensive colon involvement running an acute course and terminating in death with very little lung involvement.

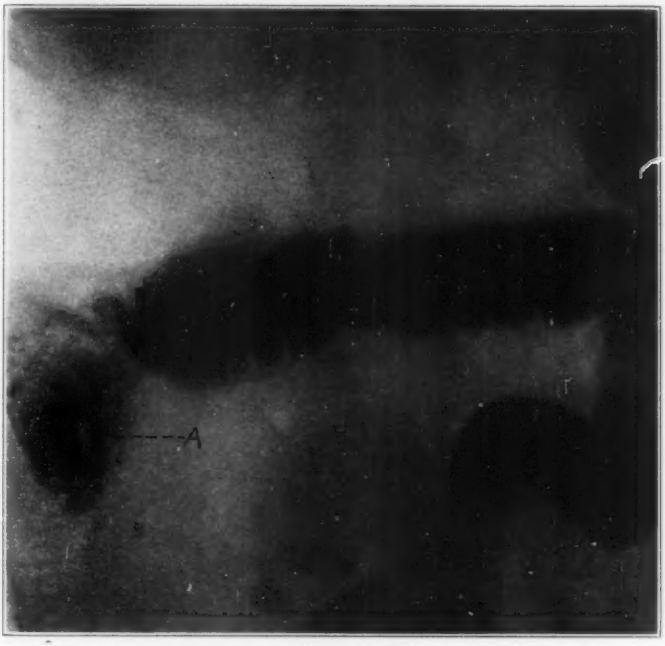

FIG. 2.—Incomplete filling of cecum at "A."

Our paper is based on a study of 80 cases of tuberculosis, examined roentgenologically: 70 of these are patients at the Onondaga County Tuberculosis Sanitarium, the majority having fairly well-advanced lesions. We have also in our routine work examined about 4000 patients and have especially during the past year observed the colon very carefully.

Technic. With few exceptions the barium enema (Holzknecht's formula) was employed. If the entire colon filled we assumed

[9] Roentgenology of Tuberculous Entercolitis, Jour. Am. Med. Assn., May 15, 1920, p. 1371.

[10] München. med. Wchnschr., October 23, 1906, p. 2090.

that the case was negative, although we knew that slight lesions might be present despite a completely filled colon. Those cases which failed to fill we had to return for an opaque meal, which consisted of four ounces of barium suspended in a pint of malted milk thickened with cornstarch. Six hours later the patient presented himself for observation, having abstained from food in the interval. Observations were made at half-hour intervals until

FIG. 3.—Barium enema. Absence of physiologic shadow at "A."

we were satisfied that the cecum either could or could not be filled. We only classed those cases as positive which gave an incomplete filling by both methods. With the enema, pressure with the palpating hand fails to keep the barium in the involved portion of the colon. When it is forced in, as soon as the pressure is removed, it rapidly shoots out, the uninvolved portion remaining filled. All patients were examined fluroscopically and plates were taken as a matter of record.

At Trudeau Sanitarium, Brown and Sampson prefer the barium meal, while Carmen at the Mayo Clinic, on the other hand, prefers the enema, claiming that small filling defects can better be determined by this method. In our work we found no discrepancy in the two methods. Of our 80 cases, 12, or 15 per cent, were positive, showing a definite filling defect in the cecum or ascending colon. In our 4000 non-tuberculous cases we were not always

FIG. 4.—Mouth filling. Filling defect at "A."

able to visualize a completely filled colon, but in each instance there was a definite reason for the failure, like carcinomatous infiltration, adhesions or pressure from a neighboring tumor. Also in achylia gastrica, after a barium meal, in cases associated with diarrhea we encountered a distinct hypermotility, and as a result the barium was forced along so rapidly that a completely filled cecum could not be observed. A contrast enema, however, accomplished this and differentiated the condition from intestinal tuberculosis. We

believe with Stierlin,[11] etc., that the filling defect is the most important roentgen sign of cecal tuberculosis. How much of the deformity is due to infiltration and how much to reflex spasm cannot be determined by the roentgenologist. When marked thickening and contraction have taken place there may be obstruction.

We were surprised by the frequency of gastric hypomotility, barium frequently remaining in the stomach seven and eight hours after the ingestion of the meal. This has a practical bearing on the treatment of pulmonary tuberculosis, as a few years ago forced feeding was considered an essential element for recovery. To force-feed a stomach unable to dispose of an ordinary meal is

FIG. 5.—Mouth filling. Filling defect at "A."

illogical. The overfilled stomach may cause the anorexia, distention and fermentation so frequently complained of, and explains why these patients give up one article of food after another, believing that it is the food eaten at the last meal which causes the disturbance, whereas in reality it is due to the fermentation of the food remaining in the stomach from previous meals that is at fault. The meal must not be greater than the stomach can propel into the small intestine before the next meal is partaken. In our contrast enema studies we were impressed by the frequency of the ileocecal incompetency (25 per cent). In 70 per cent there was a marked ileal stasis. All of our positive cases were sensitive

[11] Loc. cit.

in the cecal region, but in none was a definite tumor palpable. In the symptomatology our patients volunteered the information that they felt weak and prostrated after a bowel movement, and also that the odor of the stool was very foul and penetrating.

In their first report, Brown[12] and Sampson laid considerable stress on hypermotility of the colon as a sign of tuberculous colitis. There is, however, no true hypermotility but rather a rapid passage of the colonic contents through the involved area, due to rigidity of the infiltration or the contraction of the spasm.

It must, however, be borne in mind that roentgenology does not diagnose tuberculosis of the intestines, as the same findings occur in cancer and ulcerative colitis as mentioned by Stierlin.[13] Roentgenology should not be required to make a pathologic diagnosis. This should be reserved for the pathologist. Roentgenology is nothing but inspection, and as such is a part of clinical medicine. Sufficient evidence is now at hand, however, to warrant the inference that a filling defect in the cecum or ascending colon in a person afflicted with tuberculosis and associated with gastrointestinal symptoms is almost always indicative of tuberculosis of this area. We have then in roentgenology a very important aid in the diagnosis of tuberculous colitis. The importance of the early diagnosis cannot be overemphasized, as only then can treatment be of avail. Mild lesions sometimes heal spontaneously. Drugs are of no value. Surgery in the hands of qualified operators has given very satisfactory results. Even in advanced cases the recent reports of Archibald[14] and Patterson[15] emphasize this. Roentgen ray, radium and more recently heliotherapy in the form of the quartz lamplight are being used extensively, the latter especially at Saranac.

We wish to take this occasion to express our thanks to Dr. H. J. Brayton for the privilege of examining the patients at the Onondaga County Tuberculosis Sanitarium, which forms the main basis of this paper.

[12] Loc. cit. [13] Loc. cit. [14] Loc. cit.

[15] Intestinal Tuberculosis, Am. Rev. Tuberc., 1920, **4**, 433; Albany Med. Ann., 1920, **41**, 285.

REVIEWS.

A Text-Book of Practical Therapeutics. By Hobart Amory Hare, M.D., LL.D., B.Sc., Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College of Philadelphia; Physician to the Jefferson Medical College Hospital; one-time Clinical Professor of Diseases of Children in the University of Pennsylvania; Commander U.S.N.R.F. Eighteenth edition. Pp. 1033; 144 illustrations. Philadelphia and New New York: Lea & Febiger, 1922.

Alterations and additions to this well-known work have resulted in a book containing fifteen pages more than the seventeenth edition. The grouping of donors for transfusion is discussed at some length and a detailed description of the method of transfusion with citrated blood is given. A paragraph is devoted to the use of quinidine in auricular fibrillation, silver arsphenamine in syphilis, and thyroxin in cretinism. Directions are given for the preparation of solutions of gum acacia for intravenous use, and the treatment of chronic nephritis is taken up in more detail than in the previous edition. J. H. A.

A Treatise on Hygiene and Public Health. By Birendra Nath Ghosh, F. R. F., Pand S. (Glasg.); F.R.S.M., Examiner in Hygiene and Pharmacology, University of Calcutta, etc., and Jahr Lal Das, D.P.H., Member of the Royal Sanitary Institute. Fourth edition. Pp. 507; 62 illustrations. Calcutta: Hilton & Company, 1921.

The twenty-four chapters of this little book are chiefly concerned with the usual topics of water, air, soil, food, climate, sanitation of houses, schools, villages, etc. Although there is a natural undercurrent of the Indian aspects of public health, it affords much of interest to one who is not specializing on this subject. To the specialist there can be little of value, beyond a few local topics, such as Chapter VIII on "Diet in India," occasional sections on malaria, plague and similar diseases, and the local methods of building, personal hygiene and disposal of the dead. Discussion

of the action of alcohol and Pettenkofer's views on the spread of enteric, the omission of such recent developments as the relation of lice to trench fever, etc., indicate that the book has not been kept strictly up to date in successive editions, but the total absence of references make this a difficult matter to estimate accurately. The index also is far from complete. E. B. K.

HYGIENE OF WOMEN AND CHILDREN. By JANET E. LANE-CLAYPON, M.D., D.Sc. (Lond.), Dean and Lecturer on Hygiene in the Household and Social Science Department, King's College for Women. Pp. 339; 71 illustrations. London: Henry Frowde, Hodder and Stoughton, 1921.

THIS exceedingly interesting book on the hygiene of women and children represents the outgrowth of the gradual development of communal hygiene into the individual practices of such rules and modes of living as are prone to protect and prolong life under the most felicitious circumstances. Such teaching as is found in the book may probably be found in larger specialized volumes elsewhere, but its collection into one volume in an easily read text, copiously illustrated, has not been done previously. One follows in a very logical order through general sanitation to house sanitation, individual hygiene of the woman, mother and infant, with chapters interspersed on such subjects as the collection and storage of foods, beverages, milk, artificial feeding, notes on rickets and scurvy, and the care of young children. All this information is in a simple and practical form which should make the book an invaluable manual for the use of the sanitary inspector, the visiting nurse, the teacher, and it may be thoroughly recommended, in addition, as a book to be placed in the hands of parents and any one whose activities are devoted to the betterment of the living conditions of women and children. P. F. W.

STUDIES IN PALÆOPATHOLOGY. By SIR MARC ARMAND RUFFER, M.D., Late President of the Quarantine Council of Egypt, etc. Edited by ROY L. MOODIE, Ph.D., Associate Professor of Anatomy in the University of Illinois. Pp. 372; 71 plates. University of Chicago Press, Chicago, 1921.

THE term palæopathology was first used in medical literature by the author of these studies, to describe the subject to which he has made such interesting and valuable contributions. He defines it as the science of the diseases which can be demonstrated in

human and animal remains of ancient times. The greater part of the work was done in Egypt, where he served for many years (1901-17) as president of the Sanitary Council. He began by preparing microscopic sections of various parts of mummies. Only after many experiments was he able to get the tissues to the right degree of consistency for embedding in paraffin, cutting on a rotary microtome and staining. In such histological sections he could recognize the cross striations of voluntary muscle fibers from subjects three thousand years old. The main characteristics of bloodvessels, of nerves and of the heart were surprisingly well preserved. The microscopic specimens thus prepared varied greatly in the amount of detail which they showed, and this fact probably depended chiefly on the original method of preservation of the bodies, whether by some method of embalming or by simple drying. In favorable preparations he could identify the layers of the skin, the glomeruli and tubules of the kidney, the coats of intestine, as well as liver, bone, and other structures. He then in a similar way studied pathological lesions in more ancient mummies, some as old as eight thousand years. Here he found atheromata of the aorta and of other arteries; in different specimens of lungs, he saw anthracosis, hepatization of pneumonia and numerous bacilli; in kidneys, he found multiple abscesses with well-staining bacilli, and in two mummies of the twentieth dynasty (1250-1000 B.C.), he found numerous eggs of Bilharzia hæmatobia. He continued his studies of arteriosclerosis. The etiology of this condition he considers very obscure, as no tobacco was smoked and alcohol was not used to excess. In support of his theory that alcohol had not necessarily anything to do with the condition, he quotes his own experience of having made during the Mussulman pilgrimages, over eight hundred postmortems on people who had certainly never touched alcohol during their lives, and he found the condition just as common in them as in people who take alcohol regularly. He described a case resembling smallpox, but the pathological evidence is not convincing. Diseases of the bones and teeth show themselves distinctly and in several forms. No syphilitic bones or teeth were ever observed. However, arthritis deformans, spondylitis, tuberculous lesions, bony tumor of pelvis and lesions of pyorrhea alveolaris were found. This book will appeal to all pathologists and to a certain number of antiquarians. In it the researches of science link the distant ages of early Egypt with the present day in disease, in malformation and in suffering. That the study of the mummies should reveal all this is not surprising, but that the perseverance and enthusiasm of man should accomplish this study is more a matter for wonder. The illustrations add greatly to the vividness of the subject, and a chronological appendix is valuable for localizing the ages of the various remains.

W. H. F. A.

THE HEART RHYTHMS. By PAUL DUDLEY LAMSON, M.D., Associate Professor of Pharmacology, Johns Hopkins University. Pp. 98; 52 illustrations. Baltimore: Williams and Wilkins Company, 1921.

THIS valuable little book deals with the cardiac arrhythmias in a concise, logical and readable manner. No attempt is made to present any new observations, nor are symptomatology or treatment discussed. The work deals almost exclusively with the mechanism and recognition of normal and abnormal rhythms. Noteworthy points in the author's treatment of the subject are his classification of rhythms according to the point of origin of the contraction impulse, and the diagrammatic division of the heart into four functional areas. The characteristic electrocardiographic complex of each area is shown, together with the rhythms which may result from the contraction impulse originating here. The chapter upon the interpretation of the electrocardiograph might with advantage have been made more complete, yet sufficient is said to aid the beginner in interpreting tracings, and not enough to confuse. The polygraph and sphygmograph are discussed at greater length and the directions for making and interpreting polygraphic tracings are given with admirable clarity. The author feels that since through the electrocardiograph the whole subject of the cardiac rhythms has been clarified, and the interpretation of polygraphic tracings put upon a more scientific basis, it is now time for the polygraph to come into more universal use with the general practitioner who needs such a compact, portable, and relatively inexpensive instrument rather than the electrocardiograph. The book is well worth reading, and will appeal especially to students and teachers of cardiology as well as to the general practitioner.

J. H. A.

DISEASES OF THE SKIN. By RICHARD L. SUTTON, M.D., Professor of Diseases of the Skin, University of Kansas School of Medicine; Former Chairman of the Dermatological Section of the American Medical Association; Assistant Surgeon, United States Navy, Retired; Dermatologist to the Christian Church Hospital. Fourth edition. Pp. 1132; 969 illustrations. St. Louis: C. V. Mosby Company, 1921.

THE present fourth edition of Sutton's *Diseases of the Skin* is larger by forty-eight pages than its predecessor, and the total number of illustrations are increased by fifty-nine over the previous edition. Syphilis along its various lines has been amplified. The progress made in the study of the various fungus diseases is recorded in greater detail. Various dermatological conditions such as no-

cardiosis, Vincent's disease, dermatitis dysmenorrheica, amebiasis cutis, and neurotic excoriations of the skin have been transferred to new headings. The readers of the volume who wish to carry their investigations further will be assisted by the six hundred and forty additional references to dermatological literature. The present edition carries out the wishes of the writer in regard to practical treatment and amplification of cutaneous pathology. The profusion of excellent illustrations makes the volume virtually an atlas in addition to a text-book. The reviewer believes that there is no better American text-book today on dermatology than Sutton's excellent volume. F. C. K.

DISEASES OF THE SKIN. By HENRY W. STELWAGON, M.D., Ph.D., Late Professor of Dermatology in the Jefferson Medical College; Late Consultant to the Dermatological Department of the Philadelphia General Hospital; to the Howard Hospital; to the Pennsylvania Institution for the Deaf and Dumb; to the Pennsylvania Institution for Feeble-minded Children; and to the Widener Memorial Training School for Crippled Children; Late Member of the American Dermatological Association; Late Honorary Member of the Society of Dermatology and Syphilography of Italy; Late Associate Member of the Society of Dermatology and Syphilography of France; of the Vienna Dermatological Society, and of the Berlin Dermatological Society; and HENRY KENNEDY GASKILL, M.D., Attending Dermatologist to the Philadelphia General Hospital and Member of the American Dermatological Association. Ninth edition. Pp. 1313; 401 text-illustrations and 29 colored and half-tone plates. Philadelphia and London: W. B. Saunders Company, 1921.

THE last edition, the eighth, of Dr. Stelwagon's excellent book *Diseases of the Skin*, appeared in October, 1916, and the present edition, the ninth, is dated July, 1921. Owing to the death of Dr. Stelwagon, in October, 1919, a change in authorship proved necessary and the preparation of the present edition was placed in the capable hands of Dr. Henry K. Gaskill. It is always a difficult matter to carry out the ideas and style of an originator and the present author has succeeded admirably in effacing himself and bringing before the public the idea that this is the dermatological treatise of Dr. Stelwagon rather than the present compilator. According to the author, "A great part of the value in Dr. Stelwagon's treatise lies in his meticulous search for references," and many additional articles are quoted in the text and mentioned in footnotes in the present work. Various new conditions of the skin are described, such as acrodermatitis hiemalis, endothelioma, espundia, keratolysis

exfoliativa, amebiasis cutis, and folliculitis ulerythematosa reticulata. Seventy-four new illustrations have been added and a few of those formerly employed have been eliminated. The volume still maintains the excellence of former editions. F. C. K.

SYNOPSIS OF MIDWIFERY. By ALECK W. BOURNE, B.A., M.B., B.Ch. (Camb.), F.R.C.S., (Eng.), Obstetric Surgeon to In-Patients, Queen Charlotte's Hospital; etc. Second edition. Pp. 295; New York: William Wood & Company, 1921.

THIS small volume is frankly intended for a means of rapidly reviewing obstetrics in case of a student or practitioner brushing up for final collegiate or licence examinations. The preface states that in this, the second, edition there have been some changes in the subjects of toxemias of pregnancy and hemorrhages. The abridgment of the subject-matter has been well done. The next presents the essentials of obstetrics in crisp, concise sentences. There is no discussion, and a middle-of-the-road attitude is taken in disputed points. The book is a good manual for a rapid *resume* of the subject. P. F. W.

NUTRITION AND GROWTH IN CHILDREN. By WILLIAM R. P. EMERSON, Professor of Pediatrics, Tufts Medical College. Pp. 342; 56 illustrations. New York and London: D. Appleton & Company, 1922.

THE writings of the author upon the subjects of nutrition and growth are well known. Many of his papers have appeared in medical literature and not a few in magazines devoted to circulation among the laity. In the present volume will be found a complete and practical survey of Dr. Emerson's work. It would seem that this book is intended for use for parents, teachers and social workers as well as for medical men. In the preface one finds mention of the first nutrition class which was organized in 1908 by Dr. Emerson at the Boston Dispensary. From this beginning the work has spread so that the present time sees special clinics and classes throughout the country, all of which are modelled to a large extent along the lines which are clearly set forth in the book under discussion. The twenty-eight chapters are presented in three sections—the diagnosis of malnutrition, malnutrition and the home, a nutrition program for the community. The underlying principle set forth is that there are five chief causes of malnutrition which must be looked for and corrected. In order of importance these are—physical defects,

especially nasopharyngeal obstructions; lack of home control; overfatigue; improper diet and faulty food habits; faulty health habits. It will be noted that improper diet comes fourth on the list and this position is well supported by the arguments presented. In the diagnosis of malnutrition the relation of weight to height is taken as an accurate standard. It should be mentioned that the illustrations are excellent and to the point.

A. G. M.

TUMORS, INNOCENT AND MALIGNANT. By SIR JOHN BLAND-SUTTON, L.D., F.R.C.S., Consulting Surgeon to the Middlesex Hospital. Seventh edition. Pp. 806; 383 illustrations. New York: Paul B. Hoeber, 1922.

THE medical profession should by this time be so well acquainted with this important book that little comment is needed upon the appearance of a new edition. Though "old fashioned" in its presentation of the subject, in the character of its illustrations and in its comparative neglect of histological details, it nevertheless continues to be of value to physician, surgeon and pathologist alike, on account of its wealth of illustrative material and case reports and the sound judgment of the thoughtful and experienced author. Almost half the references are to publications of the preceding century. Exception might be taken to various details of tumor classification and prognosis, but with the present lack of agreement on these topics this could hardly be otherwise. Radiotherapy is given but scant attention, so that one is not surprised to find lukewarm and rather vague recommendations that were more frequent in the previous decade than at present. Also one is forced to disagree with the statement on page 281 that "it is impossible without injury to the skin to administer a sufficiently strong exposure to influence malignant tumors of the viscera." A list of illustrations in this book is especially needed. The use in the index of black-face type for the main items is a detail well worth publishers' attention.

E. B. K.

CLINICAL ELECTROCARDIOGRAPHY. By FREDERICK A. WILLIUS, B.S., M.D., M.S. in Medicine, Section on Clinical Electrocardiography, the Mayo Clinic, Rochester, Minnesota, and the Mayo Foundation, University of Minnesota. Pp. 188; 185 illustrations. Philadelphia and London: W. B. Saunders Company, 1922.

To the reviewer it would appear that this book has a number of serious faults and is not up to the high standard set by other works

on clinical electrocardiography. One-sided statements of debatable points are made (as in the discussion regarding the significance of the T-wave). The classification of abnormal cardiac mechanisms is artificial and has no advantages that are apparent. The description of auricular flutter as an acceleration of the auricles to a rate beyond 200 a minute, reveals how remarkably little the author has been influenced by the recent work of Lewis on this subject. A number of the tracings (Figures 48, 52, 57, 60 and 64) are susceptible of interpretations other than those ascribed by the author, while in Figures 54, 58, 62 and 76, errors in interpretation are noted.

On the credit side may be placed the follow-up statistics of patients who had shown various abnormalities in their electrocardiograms and the excellent collection of tracings of patients with angina pectoris. C. C. W.

THE PLACE OF VERSION IN OBSTETRICS. By IRVING W. POTTER, M.D., F.A.C.S., Obstetrician to the Deaconess, St. Mary's, City, Columbus, Homeopathic and Salvation Army Hospitals of Buffalo. Pp. 133; 42 illustrations. St. Louis: C. V. Mosby Company, 1922.

WHETHER the place of version in obstetrics is or is not to be made the routine method of delivery of all cases capable of being delivered by the natural passages rests upon the personal convictions of the individual operator. Potter believes the form of version which he has perfected should supplant the mechanism of normal labor. This excellently illustrated monograph, which may be studied with profit, is a very clear and detailed exposition of the Potter version. P. F. W.

THE CLINICAL STUDY OF THE EARLY SYMPTOMS AND TREATMENT OF CIRCULATORY DISEASE IN GENERAL PRACTICE. By R. MCNAIR WILSON, M.B., CH.B., late assistant to SIR JAMES MACKENZIE under Medical Research Committee; late Cardiologist, War Office Trench Fever Committee; Consulting Physician, Ministry of Pensions. Pp. 245; 111 illustrations. London: Henry Frowde, Hodder and Stoughton, 1921.

THE book commences with a brief foreword by Sir James Mackenzie. An introduction then expounds the author's main hypothesis, namely, that stimulation of the vagus may reflexly stimulate the sympathetic and thus lead to a sympathetic reaction, the end result being quickening of the pulse instead of the expected slowing.

Observations made by the author upon himself, his friends, his patients and soldiers suffering from trench fever are then invoked

in abundance to prove his hypothesis and to emphasize the importance of such factors as intestinal stasis, improper breathing and toxin states in producing certain morbid conditions. These morbid conditions are described largely in terms of vagus or sympathetic activity and include breathlessness, cyanosis, exhaustion, headache, hyperalgesia, pain, tachycardia, fever and other similar conditions. The book abounds in repetitions, and one feels after reading it that one has accompanied the author through many tedious observations and explanations, but carried away very little of value regarding the early symptoms and treatment of circulatory disease in general practice. J. H. A.

LEHRBUCH DER GRENZGEBIETE DER MEDIZIN UND ZAHNHEILKUNDE. By JULIUS MISCH, dentist, Berlin, with the collaboration of a number of physicians. Second edition. Two volumes, pp. 1363; 351 illustrations. Leipzig: F. C. W. Fogel, 1922.

THIS book is stated to be for students, dentists and physicians. The various sections of the book are written by physicians in conjunction with Dr. Misch and apparently the effort has been made to present the subject-matter from the viewpoints both of physicians and dentists. The oral and particularly the dental manifestations of the various ills the body is heir to are exhaustively discussed, as well as the general effects of disorders of the teeth. The many illustrations, for the most part, are excellent.

There has been real need for a book of this sort and it has already enjoyed a deserved popularity in Germany. Its usefulness could be increased by the elimination of a great deal of unnecessarily lengthy discussion of the diagnosis and treatment of systemic diseases. C. C. W.

SURGICAL CLINICS OF NORTH AMERICA. VOL. I, NO. 6 (NEW YORK NUMBER). Pp. 295; 122 illustrations. Philadelphia and London: W. B. Saunders Company, 1922.

THIS number of the Clinics is an especially interesting one, taking up, as it does, thoracic surgery, cord surgery, some features of abdominal surgery and miscellaneous subjects. The contributors are all men well known in their line and in most instances the subjects chosen by them for this publication express the direction of their chief accomplishments. For this reason the reader probably gets the very best data on that particular condition and its treatment.

It is exceedingly interesting and instructive reading and shows very well the steady improvement and advance in surgical diagnosis and technic. E. L. E.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Hemosiderosis of Pernicious Anemia.—McMaster, Rous and Larimore (*Jour. Exp. Med.*, 1922, **25**, 521) point out that in recent years pernicious anemia has been thought by many to be due to an injurious agent derived from the gastro-intestinal tract. One of the findings which has been considered well-nigh conclusive in support of this idea is the marked siderosis of the liver parenchyma, which has been taken to indicate that pathological blood destruction is localized within the portal tributaries. They show experimentally that this hemosiderosis is inconclusive evidence of blood destruction within the portal system. Young rabbits were injected subcutaneously with varying amounts of rabbit hemoglobin on six days out of every seven. The injection periods ranged from thirteen to one hundred and two days, the hemoglobin dose from $\frac{1}{4}$ of that normally possessed by the animal to $\frac{1}{150}$ of it. The liver, kidneys, spleen and red bone marrow were studied with reference to their hemosiderin content. The following results were obtained. The distribution of the hemosiderin depended on the amount of hemoglobin given. No siderosis occurred when a daily portion less than $\frac{1}{90}$ was employed. When slightly larger doses were used over long periods of time a siderosis of the liver occurred, similar to that in pernicious anemia, whereas the kidneys were non-pigmented or negligibly so. When more hemoglobin was used the differences in the organs became less noteworthy and when very large injections were given resulting in hemoglobinuria after but a few days, the epithelium of the renal tubules was heavily pigmented and the liver cells by con-

trast negligibly so. In these experiments they show that the constant presence in the general, as distinct from the specifically portal, circulation of a small amount of free hemoglobin, leads eventually to a siderosis of the liver similar to that which has been considered so significant in pernicious anemia. When this amount is kept within certain limits, renal siderosis fails to appear or is negligible in degree. When more is given the epithelium of the renal tubules rapidly becomes pigmented, the iron deposition far outstripping that in the liver. Their conception of the phenomenon is that the liver is able to remove free hemoglobin from the blood stream, and normally is probably the organ which keeps the plasma free of hemoglobin. When the hemoglobin coming to it is increased, it may still receive it but in so doing become siderosed. When hemolysis is considerable the liver is overtaxed and the pigment accumulates in the blood and is dealt with by the kidneys according to its threshold of excretion. The hemosiderin passes readily through the glomeruli but undergoes a greater or less resorption during its passage through the tubules and renal siderosis comes about. They believe that the variations in distribution of hemosiderin in pernicious anemia are rendered understandable by these facts.

Tularemia Francis 1921. A New Disease of Man.—FRANCIS' (*Jour. Am. Med. Assn.*, 1922, **78**, 1015) report has to do with one of a series of most important observations which have been carried on by McCoy and his associated of the United States Public Health Service, the impetus for which was received during the fight against plague in California in 1911. At that time McCoy recognized a plague-like disease of rodents, which was differentiated from true plague, and of which tularense was later found to be the etiological agent. This plague-like disease has been found in squirrels, rabbits and guinea-pigs, being transmitted by various insects. Of importance to the profession is the discovery that this disease occurs in man from sources of infection in California, Indiana and Utah and that it is readily contracted by laboratory workers intimately associated with experimental work upon this infection. When the disease is contracted by insect bite it is characterized by a well-marked reaction at the site of infection, which is followed after a brief incubation by lymphadenitis of the regional glands, chills and fever and prostration for a period of from one to four weeks. Laboratory workers contracted the disease without obvious sites of infection; they all showed a sudden onset of fever, without other definite manifestations, which lasted with remissions about three weeks. All of the trained workers of the service who were immediately concerned with the investigation had the infection and showed characteristic immunological reactions. Francis points out that "the ready susceptibility of man to this infection in Nature and in the laboratory, its wide prevalence in Nature in a number of rodents, and the growing number of blood-sucking insects found capable of conveying the infection, should combine to put the medical profession of the United States on the watch for cases of this new disease of man."

Length of Life of Transfused Erythrocytes.—WEARNN and his coworkers (*Arch. Int. Med.*, 1922, **29**, 527), using the technic devised by Ashby determined the duration of the existence of Group IV trans-

fused red blood corpuscles in the circulation of patients whose blood belonged to Group II. Four cases of pernicious anemia and four of anemia secondary to nephritis were studied. The last of the transfused red blood cells disappeared from the circulation in from fifty-nine to one hundred and thirteen days, with an average of eighty-three days. No difference was noted between the duration of the stay of the transfused cells in the circulation of patient with primary and secondary anemia. One of the cases of pernicious anemia (Group II) was transfused with blood from another case of pernicious anemia (Group IV) and in this instance the transfused cells behaved as did the corpuscles from normal donors.

SURGERY

UNDER THE CHARGE OF

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A Consideration of the Relative Merits of Resection and Gastro-enterostomy in the Treatment of Gastric and Duodenal Ulcer.—De Quervain (*Surg. Gynec. and Obstet.*, 1922, **34**, 1) says that he has abandoned schematic gastro-enterostomy and leans more toward resection. Ninety per cent of ulcer recurrences, peptic ulcer and other disturbances, occur in the first four years after operation, so that statistics which depend on results reported earlier are apt to show too favorable results. Simple gastro-enterostomy produces in all forms of gastric ulcer about the same early results—somewhat more than four-fifths cure or improvement approximating cure. In ulcers at a distance from the pylorus the average results are no less favorable than in those at the pylorus. With sleeve resection, there is no late bleeding from the ulcer with the resultant occasional death and the danger from peptic ulcer is almost *nil*.

Benign Tumors of the Stomach.—Eusterman and Senty (*Surg Gynec. and Obstet.*, 1922, **35**, 5) say that benign tumors of the stomach are rare and constitute only 1.3 per cent of all gastric tumors that have come to operation. The actual proportion of benign new growths to malignant new growths or ulcerations is as 1 to 200. Myomata and fibromata constitute the largest group, gastric polyposis the most infrequent. About 50 per cent of benign tumors are found in patients more than forty years old. There is no characteristic syndrome and gastric chemism ranges from achylia to hyperacidity with hypersecretion. The summation of evidence favors the diagnosis of gastric cancer. The majority of tumors are situated in the region of the pylorus, the greater curvature, anterior and posterior walls. The smaller tumors are

practically symptomless unless situated at the orifices or unless multiple. Common complications are recurring hemorrhage and pyloric obstruction. Palpable mass and food retention are less frequent than in gastric cancer.

Essential Hematuria.—LEVY (*Surg. Gynec. and Obstet.*, 1922, **34**, 22) says that the diagnosis of essential hematuria should be made only when all known urological methods have been employed with negative findings for it is purely a clinical diagnosis indicating renal bleeding of unknown etiology. In 36 per cent of the cases, the onset of the hematuria occurred in the fourth decade of life. The bleeding developed spontaneously in most cases and was symptomless. The right kidney was responsible for the bleeding in 17 cases and the left in 13. In no case were both kidneys involved. The results of operative procedures have not been better than those of non-operative methods. In the author's series, there were recurrences after decapsulation and two nephrotomies. Nephrectomy is the only operation ever indicated and that only as an emergency measure to save a patient from bleeding to death. Non-operative methods have been used with success, including intrapelvic injection of silver nitrate and adrenalin, the oral administration of calcium lactate and the subcutaneous or intramuscular injection of horse serum. Spontaneous cessation of the bleeding occurs frequently in essential hematuria.

Results in One Hundred Cases of Cancer of Prostate and Seminal Vesicles, Treated with Radium.—DEMING (*Surg. Gynec. and Obstet.*, 1922, **34**, 99) says that a combination of radium and surgery offers a possibility for treatment of cancer of the prostate and seminal vesicles. While operation does not diminish the amount of radium necessary to produce good results it does not increase the possibility of hastening metastases. Radium gave symptomatic relief and return of normal urination in 75 per cent of the cases. Moreover, radium relieved the pain in the back in 50 per cent of cases suffering from metastases. Irritation from radium can be avoided by treating widely remote areas in successive treatments and by alternating between rectal, urethral and vesical applications. At least 3000 milligram hours must be given to produce symptomatic and local results in the same patient. Cases which did not respond to radium did not receive sufficient radiation. Large doses must be given in as short a period as possible to produce maximum results. Combined extraglandular and intraglandular radiations apparently give the most satisfactory results.

Synovial Membrane Tumors of Joints.—HARTMAN (*Surg. Gynec. and Obstet.*, 1922, **34**, 161) says that the occurrence of this type of tumor in joints and especially in the knee-joint raises at once the problem of saving the limb and the function of the joint. Their development is slow as a rule and ample warning is always given in the form of pain, swelling and interference with function. They are readily removed if attacked in the early pedunculated stage without danger of local recurrence or remote metastases. For classification, it seems best to place them with the benign tumors of connective tissue origin since the giant cells are of the foreign body type and no mitosis is seen. There is however a

potential malignancy. Palliative measures and incomplete excision are contraindicated and are perhaps responsible for the malignant characteristics developed in these cases. These neoplasms should not be termed sarcoma at least until evidences of malignancy are seen either clinically or pathologically. Since any one of the characteristic cells, namely xanthoma or foam cells, pigmented cells and giant cells, may be absent from an otherwise typical case the writer prefers the name of myeloid tumor.

Carcinoma of Prostate.—BARRINGER (*Surg. Gynec. and Obstet.*, 1922, **34,** 175) says that in but 2 per cent of cases of carcinoma of the prostate seen at the Memorial Hospital, is the carcinoma confined to the prostate. Routine prostatic examination of all patients beyond the age of fifty, irrespective of symptoms is the only rational method whereby we may hope to make a diagnosis of prostatic carcinoma early in the disease, The results of radium treatment of carcinoma of the prostate are superior to operative removal both in causing regression of the disease and in coping with urinary retention.

Thyrotoxicosis.—BLACKFORD (*Surg. Gynec. and Obstet.*, 1922, **34,** 185) says that there are two points to be emphasized, importance of early diagnosis in order to obtain a cure by surgical removal of a toxic goiter before permanent damage is done the patient. The mortality from removal of non-toxic or mildly toxic cases is almost zero in competent hands. Second, a badly damaged heart from goiter intoxication does not contraindicate surgery. Practically speaking, the cardiac reserve of the patient can be improved by treatment until good enough to withstand operation. The bulk of surgical mortality occurs in badly toxic cases, not in the extreme cardiopaths.

Histology and Mortality in Cases of Tumor of the Bladder.—SCHOLL (*Surg. Gynec. and Obstet.*, 1922, **34,** 189) says that 41 per cent of all patients operated on for malignant papillomata are alive on an average of three years after operation while only 11 per cent of patients with solid carcinoma have lived more than three years after operation. The incidence of recurrence following operation on patients for solid carcinoma is much greater than that for malignant papillomata. Squamous-cell carcinomata of the bladder are extremely malignant and rapidly fatal while adenocarcinomata are about as severely malignant as papillomata. Simple angiomata of the bladder may grow so large as to cause obstruction. Myomata of bladder often grow very large. Myxomata occur generally in young persons. Sarcoma is probably the rarest and most malignant of vesical tumors. It occurs in middle-aged persons, metastasizing extensively with tendency to rapid recurrence.

Duodenal Ulcer in Infancy.—PATERSON (*Lancet*, January 14, 1922, p. 63) says that duodenal ulcer is a rare condition in infants but more careful examination of the duodenum in marasmic infants may show it to be more common than is at present admitted. Ulcers may be present in melena neonatorum. In older infants, they may follow on any gastro-intestinal upset. They may certainly complicate extensive septic burns or septicemia. Tuberculosis is the common cause of

duodenal ulcers in older children. The diagnosis of duodenal ulcer is difficult and usually not made. Duodenal ulcer may be successfully treated by operation.

Ulcer of Lesser Curvature of Stomach.—FABER (*Lancet*, January 14, 1922, p. 65) says that gastric ulcer in the corpus of the stomach (on the lesser curvature) is commoner in women than in men. Juxtapyloric ulcer is more frequent in men than in women. Gastric ulcers are chiefly ulcers of the corpus in women, and juxtapyloric ulcers in men. Statistics of postmortem examinations show that gastric ulcer is commoner in women than in men. Ulcer of the corpus may therefore be assumed to be the more frequent variety. On account of their symptoms and course, juxtapyloric ulcers make easier subjects for surgical treatment than ulcers of the corpus. For this reason, statistics of operative material so often show a preponderance of men. Ulcer of the corpus, which might be called the women's ulcer, has a more favorable course than the juxtapyloric. It heals more readily and the raw ulcer found postmortem has more often than the juxtapyloric, the character of a fresh acute ulcer. Ulcer of the corpus often lacks the symptom-complex so characteristic of the juxtapyloric ulcer, especially the late pains and the hypersecretion. This obtains in the case of recent and chronic ulcer of the corpus. We may presume that a large number of ulcers of the corpus as a rule in women make their appearance and get well again without the diagnosis "gastric ulcer" being made.

Neurofibromyxoma Treated by Conservative Operation.—GATCH and RITCHEY (*Ann. Surg.*, 1922, **75**, 181) say that various authors believe that benign fibrous or fibromyxomatous tumors of nerve sheaths may undergo malignant degeneration into sarcoma. If the tumor is of long duration, it is not likely to be malignant. The presence or absence of motor or sensory paralysis is a most valuable point. A nerve will withstand a really remarkable amount of stretching or pulling from a benign growth but is quickly destroyed by the infiltration of its substance by a sarcoma. The gross appearance is significant. The encapsulation of the fibrous portion of the tumor and the possibility of shelling the same from the center of a nerve trunk would seem to be strong evidence of a benign growth, as is the lack of encapsulation with fixation of the growth to the contiguous structures strong evidence for sarcoma. The authors feel that microscopical study to the exclusion of other factors is misleading.

Ruptured Spleen.—METCALFE and FLETCHER (*Ann. Surg.*, 1922, **75**, 186) say that the healthy spleen may rupture spontaneously or from comparatively slight trauma. The symptoms at first may be slight; some dizziness, nausea or vomiting with restlessness and indefinite abdominal pains or the immediate symptoms may be severe intra-abdominal hemorrhage depending upon this contingency whether the capsule of the spleen has ruptured or remained intact, forming a large subcapsular hematoma. In the authors' cases an agonizing pain was felt in the left shoulder. They feel that it is of value in diagnosis with evidence of hemorrhage. They advocate immediate splenectomy as the only safe treatment.

PEDIATRICS

UNDER THE CHARGE OF

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Studies of Infant Feeding—A Bacteriological Study of the Feces and the Food of Normal Babies Receiving Breast Milk.—BROWN and BOSWORTH (*Am. Jour. Dis. Children*, 1922, **23**, 243) found that direct smears from the stools of normal breast-fed babies present a practically constant picture, which is characterized by an almost complete dominance of the bifidus group. In this picture cocci and Gram-negative organisms are indistinguishable or are present in very small numbers. This proportion of bacterial types may be changed by abnormal physiologic conditions. A baby who has been on cow's milk formula for several days, although originally breast-fed, may show bacteriologically the effects of this diet even as long as four weeks after the continuous ingestion of breast milk. This is indicated from the smears from the feces by a larger number of cocci and Gram-negative bacilli than is typically found as characteristic of a normal breast-milk stool. If a cow's milk formula is used before the third day after birth, and breast milk is used thereafter, the establishment of fecal types of bacteria follows the course of the normal nursling very closely. From the study of anaërobic cultures it was found that B. bifidus is also the dominant living type of organism in the feces of normal breast-fed infants. The proportion of types represented in the direct smears is closely paralleled by the proportion of types growing on anaërobic cultures. Aërobic cultures from the feces of normal nurslings typically showed a predominance of colon-aërogenes groups. This may be lessened by abnormal physiologic conditions. While the study of the fecal flora of infants by anaërobic culture seems to be of great importance, aërobic cultures should also be used as a check to determine the presence of aërobic pathogenic bacteria or of adventitous bacteria. The results obtained from the study of drawn breast milk used for supplementary bottle feedings were inclusive, since no definite relationship could be established between the types of fecal bacteria and the bacteria isolated from the milk. This was made more difficult because the babies had not had a monotonous diet which could be used as a check and because the majority of the organisms isolated from the milk were staphylococci and B. coli, which may be isolated from the normal stool. This study emphasized the fact that even a slight amount of handling may introduce types of bacteria into the feedings of a bottle-fed baby which a breast-fed infant would not ordinarily ingest. The study of the stools of normal breast-fed babies has shown that a typical monotonous flora in the feces follows the continuous ingestion of breast milk. From the examination of the breast milk it would seem that staphylococci may be ingested in all cases and that a lactic acid bacillus typical of B. bifidus may be frequently present in the milk as it comes from the breast. An important

question arises as to the identity of the bifidus-like bacillus which has been isolated from the breast milk and from the skin around the nipple. They think that it is B. bifidus and they believe that this group of organisms which are present in or on the nipples of the mother are an important source of the bifidus organisms found in the nursling's intestinal tract.

The Bacteriology of the Normal Infant's Urine.—HELMHOLZ and MILLIKIN (*Am. Jour. Dis. Children*, 1922, **23**, 309) studied the urine of 75 infants, 35 boys and 35 girls. The results of their studies emphasize the futility of obtaining evidence by the method of Langer and Soldin that in any way will help to settle the problem of the mode of infection in pyelitis. The error that creeps in by contamination, even when all precautions are taken, is such that the evidence obtained is always open to criticism. Their data show that in $\frac{3}{7}$ of the specimens obtained the urine was sterile, and $\frac{2}{3}$ of these observations were made in duplicate. They do not agree with Kleinschmidt that at each catheterization a different flora is obtained, nor with Langer and Soldin that a sterile specimen is only an accident, and that repeated catheterization will always yield bacteria in the urine. Recatheterization was repeatedly done and identical results both with regard to sterility and flora were obtained. They call attention to the types of organisms found by Kleinschmidt and by Langer and Soldin, those of the colon group and Streptococcus lacticus, which are all inhabitants of the intestinal canal and not normally present in the urethra as far as can be learned. Kleinschmidt asserts that by taking smears from the meatus after cleansing it he was able to prove the constant presence of an organism of the same type as that found in cultures of the urine. The method used by Langer and Soldin of obtaining cultures is also open to criticism since by washing out the urethra, organisms may be easily washed into the bladder. They found long chains of streptococci, which they believed to have grown from organisms coming from the kidney. The most plausible interpretation is that they were washed in from the urethral opening, and are essentially contaminations, as it is not likely that organisms would grow so rapidly in urine and not grow in more favorable culture media after inoculation. The findings of the authors are at variance with those of both Kleinschmidt and of Langer and Soldin in the frequency of occurrence of Streptococcus lacticus, which was always present in their cultures. They found it in only 6 instances, and it may have been present in 5 others, so that at most it was present in 15 per cent of the urines examined. In 6 of 11 instances the Streptococcus lacticus was found in the liquid medium and not recovered on the solid medium.

Studies of Infant Feeding: A Bacterio-chemical Study of the Acid Stools Excreted by Breast-fed and Bottle-fed Infants.—BOSWORTH, WILDER, BLANCHARD, BROWN and MCCANN (*Am. Jour. Dis. Children*, 1922, **23**, 309) describe a method for the distillation of volatile acids from the stools of infants, and also give a graphic method for the study of the nature of the volatile acids, which may be distilled by their technic. Following these procedures they have found that the stools from normal, healthy breast-fed babies are acid in reaction and contain

the volatile acids, formic and acetic. By the same technic they have found that the stools from normal healthy bottle-fed babies are acid, neutral or alkaline in reaction. The acid stools may contain very large amounts of acid and the volatile acid present is acetic acid. Bacillus aërogenes, Micrococcus ovalis, Bacillus bifidus and other unidentified organisms isolated from acid stools possess the power of reducing citrate to a volatile acid. The volatile acid produced by Bacillus aërogenes, Micrococcus ovalis and other unidentified bacteria was determined to be acetic acid. The volatile acid produced by Bacillus bifidus was found to be a mixture of acetic and formic acids. Other organisms like Bacillus coli, Bacillus capsulatus, Bacillus acidi lactici, and Bacillus cloacæ disposed of the citrate, producing carbon dioxide and water without the formation of acetic acid. If a synthetic food containing no citrate was fed to an infant, no acetic acid appeared in the stools. If a synthetic food containing a soluble citrate such as sodium citrate was fed, a small amount of acetic acid was found in the stools. If a synethetic food containing an insoluble citrate such as calcium citrate was fed, a large amount of acetic acid was found in the stools. The addition of soluble citrates such as sodium citrate and orange juice to modified milk formulas increased only slightly the acetic acid content of the stools. The addition of an insoluble citrate such as calcium citrate to modified milk formulas resulted in a marked increase in the acetic acid content of the stools. The stools from infants receiving Dryco dry milk contained large amounts of acetic acid. This was probably due to the fact that a considerable portion of the soluble citrate, originally present in the milk, was converted to insoluble citrate during the process of drying.

Potential Heart Disease and Prevention of Organic Heart Disease in Children.—St. Lawrence (*Jour. Am. Med. Assn.*, 1922, **78**, 947) studied 65 cases of potential heart disease for an average period of four and a half years. Forty-nine patients or 75 per cent remained free from evidence of cardiac disease during that time. Of 25 patients with acute rheumatic fever in this series, none contracted a lesion in the heart. Of 9 patients with myositis, bone and joint pains, the so-called growing pains and sore throat, none contracted a lesion of the heart. Sixteen patients or 25 per cent contracted a cardiac lesion while under observation. In every case in which a cardiac lesion developed the clinical picture was dominated by chorea in a severe form. No patient developed a cardiac lesion in the absence of this complication. Of 41 patients with chorea in this series 16 or 39 per cent contracted a lesion in the heart. Measures of value in preventing disease of the heart are of greatest benefit when directed against acute rheumatic fever, myositis, bone and joint pains, the so-called growing pains and sore throat. Such measures have little or no value when directed against chorea. In untreated potential cases, acute rheumatic fever is the most important factor concerning disease in the heart. With the exception of mild mitral stenosis, cardiac lesions practically always occur during the active phase of a rheumatic manifestation or a period of pyrexia. In the absence of an active phase, the physical signs in the heart remain unchanged. Evidence of mitral stenosis may not appear for a year or more after the cessation of the rheumatic manifestations. It is there-

fore impossible to state at the conclusion of an attack of acute rheumatic fever or chorea that the heart was unaffected by those conditions. Heart rate may have a marked effect upon the physical signs of mitral stenosis as shown in graphic records.

The Function of the Colostrum.—Lewis and Wells (*Jour. Am. Med. Assn.*, 1922, **78**, 863) found that the blood of newborn infants, and probably of all other mammals, contains little or none of the serum protein or protein fraction known as euglobulin. This seems to be supplied chiefly by the colostrum, which differs from milk in containing a large amount of this protein secreted directly from the blood. Euglobulin is the only blood protein that appears in the colostrum, and it is the only protein fraction in which the new-born infant's blood is deficient. Evidently the colostrum is formed to provide the fetus with a supply of euglobulin for its blood, during the short period immediately after birth when proteins may be best absorbed without disintegration by digestive proteolysis. The importance of this lies in the fact that the protective antibodies of the blood are found associated with the euglobulin fraction, and that the quantity of protective antibodies found in the colostrum, the milk and the infant's blood varies directly with the euglobulin content of these fluids. Evidently the colostrum furnishes to the new-born mammal protective antibodies, which probably adds much to its capacity to resist infection in early life. If the infant does not receive colostrum it acquires euglobulin in its blood much more slowly, and is presumably in corresponding degree less resistant to infection. It is not probable that there is any equivalent substitute for human colostrum for new-born infants.

Diagnostic Value of Determining Vital Capacity of Lungs of Children.—Wilson and Edwards (*Jour. Am. Med. Assn.*, 1922, **78**, 1107) adopted a simple method and technic for the determination of the vital capacity in children from six to sixteen years of age. A normal standard of 1.93 liters per square meter of surface area was established from a study of 362 children. A plus or minus 10 per cent deviation was allowed, thus giving a normal range of from 1.74 to 2.12 liters. The vital capacity may be read at sight from a chart in liters per square meter of surface area and in percentages of normal capacity. A normal standard of 15.5 cc for each centimeter in height was also indicated as another method of relating vital capacity measurement. An analysis of some of the factors expected to influence vital capacity measurements revealed that boys show a vital capacity 6 per cent greater than girls. The extremes of age gave values at the lower and the higher limits of the normal range established. The colored race showed a definitely lowered vital capacity. Poverty, environment and social status did not seem appreciably to influence the lung capacity. Activity and athletics tended to increase the vital capacity. Malnutrition and underweight for height did not lower the vital capacity. Overweight for height revealed an apparent reduction of vital capacity per square meter of surface area. Vital capacity measurement was a fairly constant measurement. A reduction of vital capacity measurement of 15 per cent or more from the average normal standard should be taken as an index for the need of further examination and study of the child to ascertain the cause of the falling below the standard.

OBSTETRICS

UNDER THE CHARGE OF

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Pregnancy After Very Severe Disease of the Ovaries and Tubes.—In the *Zentralblatt für Gynäkologie*, 1922, No. 4, p. 139, ARNOLD describes the case of a woman, aged twenty-seven, who was admitted to hospital with bilateral salpingitis and excessive inflammation about the uterus. She was treated conservatively and examined at intervals during the next five years. These examinations showed extensive inflammation of both tubes and ovaries. The uterus was anteflexed, hard, very little movable, and there was a very considerable exudate fixing the uterus in the pelvis. On one occasion incision was made in the posterior vault of the vagina and a free discharge of pus followed, which could be traced to the right side of the pelvis. The patient was then in hospital for three weeks. At these examinations the ovaries were found prolapsed, bound down by adhesions, enlarged and very tender on pressure. So great was the exudate that the tubes could not be distinctly made out. The patient next presented herself at the hospital in the sixth month of pregnancy and desired attendance at her home in labor. She gave spontaneous birth to a living child which suffered from ophthalmia. At the last examination the uterus was movable; the adnexa seemed to be free from adhesions, and there was a scar in the posterior vaginal vault where the incision had been made.

Grape Sugar as a Stimulant to Labor Pains.—MÜLLER (*Zentralblatt für Gynäkologie*, 1922, No. 4, p. 140) has used grape sugar in 40 to 50 per cent in concentration, given in doses of 10 cc intravenously after careful sterilization, to stimulate the pains of labor. In cases where there was no mechanical obstruction to delivery but the delay seemed to arise from lack of general strength on the part of the patient an excellent result followed without injury to mother or child. In 15 cases in which this method was tried a positive result followed in 9; some effect was produced in 3, and no effect in 3. The doses first given were 10 per cent concentration, but this was increased to 50 per cent and the effect produced by this solution lasted from thirty or forty minutes to one hour. The writer calls attention to various analyses of the blood during pregnancy, showing a lack of sugar in some cases. He examined 17 patients and found the blood-sugar diminished more than one-half in these cases. It is a curious and interesting fact that extracts of the ductless glands and toxins derived from various sources, when injected in pregnant women, will produce almost similar results. This seems to result from an irritation of the sympathetic nervous system, which produces contraction in the unstriped muscle in the intestine and uterus. The merit of the sugar solution consists in the fact that it is not a poison, is entirely consumed in the body and can do no injury.

Cesarean Section.—*The Journal of Obstetrics and Gynecology of the British Empire* devotes numbers 3 and 4, Volume 28, 1921, to the subject of Cesarean section. Thirteen papers are published in this number by the obstetricians of the British Empire of widest experience in Cesarean section. This number of the *Journal* is practically a monograph upon this subject. In addition, there are book reviews and abstracts of current literature, and a description of a collection of obstetrical instruments in the Museum of the Royal College of Surgeons of England.

Space does not permit us to quote at length from these interesting and valuable papers, but we may give a summary of the various opinions and methods studied.

MUNRO KERR writes the first paper upon the indications for Cesarean section. The weakness of the present operation is the fact that it leaves behind a uterus permanently injured and liable to rupture should another pregnancy occur. Were this objection done away with, the indications for the operation could be rightly extended. The writer believes that all deliveries should be carried out in hospitals or nursing homes, and were this done, one common objection to obstetric surgery would cease. He also states that it is impossible to make the practice of obstetrics too surgical, for, like other branches of surgery, its first essential is surgical cleanliness.

Contrasting Cesarean section with pubiotomy, he believes that the latter is especially suitable for contractions at the outlet of the pelvis. By his method of estimating the size of the head and pelvis, using principally the thumb, he is able accurately to judge of the comparative size of the child and the mother. Induction of labor does not come into competition with Cesarean section, in his mind. He urges a more thorough preparation of the vagina and cervix in all suspected cases before operation. He also would, if possible, after Cesarean section, deliver the placenta through the vagina, believing that by this procedure the risks of infection are lessened.

A fibroid tumor obstructing the passage of the child from the uterus justifies Cesarean section. In ovarian tumors complicating labor, Cesarean section is rarely necessary. The tumor should be removed and the child delivered through the vagina. Should it be impossible to dislodge the tumor, then a Cesarean operation should be done. In eclampsia the only cases in which Cesarean section is justified are those where pregnancy is well advanced with no dilatation of the cervix or attempted labor, and when after six hours there is no improvement from blood-letting, intravenous saline infusion and morphine. When eclampsia develops earlier than the thirty-second or thirty-third week, vaginal Cesarean section should be performed.

The writer believes that placenta previa is peculiarly suitable for Cesarean section, and that the operation may come to be the general method of treatment in all cases of the central and marginal varieties. In the lateral, rupture of the membranes and a slight separation of the lower pole of the placenta usually suffice. In primigravidæ with central placenta previa, he believes that Cesarean section should always be practised.

In the majority of cases of accidental hemorrhage he would rely on quiet, warmth, morphine and pituitrin in doses of 1 cm. so soon as labor

pains begin. In his mind placenta previa far more often furnishes an indication for Cesarean section than does accidental hemorrhage. Where the uterus has been fixed before the pregnancy by some operation and conditions are such that vaginal delivery is impossible, Cesarean section must be done, and this is true with patients who have had the interposition operation. In elderly primigravidæ with rigid cervix, the writer would perform Cesarean section if the umbilical cord had prolapsed, in the interest of mother and child. In impacted shoulder presentation, he believes the indication for Cesarean section rarely arises. Where the child is abnormal, if it is very large and a question of size and not of deformity or malformation, Cesarean section might be indicated. In future it is probable that cases complicated by a tense retraction or contraction ring may be treated by Cesarean section, and this is true of those patients where some extraordinary rigidity or contraction of the cervix or pelvic floor makes delivery through the vagina difficult and dangerous. It is obvious that cases may arise in which the condition of the mother, whose life is threatened by some serious constitutional disease, indicates that she should be treated by Cesarean section. In general, Kerr believes that twenty years hence the accepted indications for Cesarean section will be extended even beyond the limits suggested.

Kerr describes a method of performing the operation which he practises and in which he is greatly interested. He recognizes that the uterine scar after the classic operation is unsatisfactory. He believes that a better scar can be obtained by an incision through the lower segment. To obtain an ideal result with this method, infection must naturally be avoided. Unlike other operators he incises the lower uterine segment transversely. In closing the wound he stitches the lower end of the wound with catgut but the bulk of the muscle tissue is closed with linen thread or fine silk. He takes pains to suture the uterus while in a state of retraction as distinguished from that of contraction. He believes it possible by so doing to procure better approximation, and he would always deliver the placenta through the vagina if this can be done. Occasionally in his operations it is necessary to insert a blade of the forceps or both blades to deliver the child's head. At the time of writing his paper he had operated by this method 22 times. He makes a longitudinal incision, with the patient in the Trendelenburg position, reaching from below the umbilicus to the symphysis. After the abdomen is opened the bladder is dissected off the anterior uterine wall. The transverse incision is made in the lower uterine segment and a suture placed at each end of the wound to control any laceration at the ends, and after delivery to pull up the wound so that it can easily be stitched. By passing a hand behind the uterus the child is pressed out. Sometimes one blade of the forceps is used to force out the head, very rarely both blades. When the child has been extracted and the cord tied the cord is dropped through the cervix, so that it may be a guide to the delivery of the placenta. The wound is pulled up by the two lateral stitches and the mucous membrane closed by catgut, the muscle by linen thread and a third layer of catgut to replace the bladder. A large retractor in the lower part of the abdominal wound gives easy access to the lower segment. He believes that this incision cuts through a less vascular area than the higher one; that the bleeding is extraordi-

narily slight unless the wound opens the vessels at the side; the wound is thin and easily closed. A further great advantage is the fact that the wound in this area is at rest during the early days of the puerperal period, and because the lower uterine segment does not become fully stretched until labor is well advanced, the scar is in a safer region than in the ordinary longitudinal incision. In 22 cases he has had one fatality; there has been one spontaneous delivery after the operation and on 4 cases a second Cesarean section has been done. In 2 of these cases the scar was very carefully examined and no trace was found of the former wound. In 1 of his operations the patient was at term without labor. The wall of the uterus was much thicker and the lower segment more difficult to reach. In 1 case the amniotic liquid had escaped, and the head of the child lay transversely at the pelvic outlet. After making the incision the operator could not raise the head out of the pelvis. The incision was extended longitudinally and the child was delivered.

The Relationship Between Toxemia of Pregnancy and Uterine Sepsis.—KELLOGG (*Amer. Jour. Obst. and Gynec.*, April, 1922, p. 366) has studied 400 toxemic cases to observe the relationship between toxemia and sepsis. He believes that symptoms of toxemia call for treatment so soon as discovered, and that eclampsia is never a self-limited disease. The mortality of toxemia with convulsions in hospital practice he places at 25 per cent, of whom 90 per cent died within thirty-six hours. The mortality in hospital practice of toxemia without convulsions is 2.5 per cent, a very considerable death rate. Of those toxic patients who survive convulsions, 9 per cent die of uterine sepsis. In toxemics who have no convulsions, uterine sepsis causes death in 0.5 per cent. Of unselected non-toxemic cases 2.5 per cent became septic; 14 per cent of toxemics without convulsions became septic; 25 per cent of toxemics with convulsions became septic irrespective of the method of delivery. Toxemic patients are four times as likely to become septic under similar methods of delivery as unselected and non-toxemic patients. Convulsions increase the liability to sepsis; the absence of convulsions slightly diminishes it. These patients are more likely to have difficult operative deliveries with a higher septic rate. These facts indicate that in delivering toxemic patients we should avoid, if possible, capital operations. The writer would induce labor by bags, unless he could start labor with catharsis. The patient should be allowed to deliver herself if possible, or be delivered by the application of forceps. Morphine and blood-letting should be employed as indicated. He adds a word of caution concerning the action of bags, that when the bag fails to dilate the cervix and bring on labor, it should be promptly removed and delivery completed by manual dilatation, vaginal or abdominal section. The writer states that symptoms of toxemia of pregnancy call for quick action and good judgment.

Rupture of the Scar of a Previous Cæsarean Section.—GOUGH (*Lancet*, March 11, 1922, p. 485) describes the case of a patient who had a Cæsarean operation two years before her last admission to hospital. At the previous operation the uterine wall was closed with two layers of catgut. The patient came to hospital at full time, complaining of

pain in the back and lower abdomen. She was well enough to walk, but within four hours after admission she became very ill with symptoms pointing to some intra-abdominal complication, and the abdomen was opened. A quantity of blood-stained fluid was found, and in the left broad ligament and under the utero-vesical peritoneum there was a collection of blood. It was found that this was due to the giving away of the uterine scar at its lower end. The wall of the uterus was incised at one side of the rupture and a dead child extracted. The old scar was then removed and the uterine wall closed with catgut. The patient made an uninterrupted recovery.

GYNECOLOGY

UNDER THE CHARGE OF

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Ovarian Autotransplantation.—As a result of his experience with the transplantation of ovaries in the course of gynecological surgery, GIRARD (*Calif. State Jour. Med.*, 1922, **20**, 21) concludes that autografting of ovaries is a perfectly safe and rational procedure and is indicated, except in cases of malignancy or ovaries grossly infected, in all patients requiring removal of the ovaries, with or without hysterectomy. Ovaries which require removal, in his opinion, are: (*a*) Badly traumatized ovaries with much raw surface on the capsule; (*b*) ovaries showing considerable cystic degeneration, and (*c*) ovaries having an impaired blood supply. Cystic degeneration of ovaries is no barrier to autotransplantation and ovaries removed in conditions of pyosalpinx can be transplanted, provided the ovaries themselves are not grossly infected. He believes that autotransplantation lessens and delays ablation symptoms following castration and in some cases affords complete freedom from symptoms of artificial menopause. That the autografts functionate is shown by periodic increase in size and tenderness of the grafts with amelioration of the ablation symptoms and, when the uterus remains, by menstruation. Reasonably healthy and undamaged ovaries should be left in situ with or without the uterus and autotransplantations should be used to carry on the physiological functions of the ovary only in those cases where, for reasons given above, both ovaries must be removed. The technic of autografting is simple and adds no extra risk to the operation. In all cases the ovaries are completely removed and the uterine end of the tube is resected by a V-shaped incision into the cornu of the uterus. The ovaries are wrapped in a gauze sponge and placed in normal salt solution of body tempera-

ture. After the peritoneal toilet has been completed a pocket is made by blunt dissection between the peritoneum and the under surface of the rectus muscle, on either one or both sides of the incision, according to the number of grafts to be used. The ovaries are then carefully inspected and areas of cystic degeneration are culled out after which the remainder is cut into disks 2 x 2 x ½ cm. and from one to three of these disks transplanted into the already prepared pockets. No sutures are used to hold the grafts in place. The abdominal wall is then closed in the usual manner.

Radiation Versus Surgery in the Treatment of Uterine Cancer.—The working rules that have been adopted by CROSSEN (*Jour. Missouri State Med. Assn.*, 1922, **19**, 55) are that in the advanced inoperable cases as well as in the borderline cases of uterine cancer, radium is our most effective remedy. The palliative effect is nothing short of wonderful. The enlarged carcinomatous cervix with its bleeding papillary masses melts away as if by magic and the cavity closes, largely or entirely by granulation. But it should be remembered that radium is two-edged and may do as much harm by causing excessive scar tissue contraction or actual stimulation of the cancer cells as it may do good, consequently its use requires decided caution. It is hoped that in time the curative effects of radium may be extended to the limits of the pelvis, but that ideal has not yet been attained. In some extensive cases the cancer is completely eliminated by the radium; this result is attained, however, in only a small proportion of the cases. It may be hoped for but it is so infrequent in the classes of cases under consideration that the remedy must be presented to the patient as essentially a palliative measure, with only a possibility of cure. It is advisable to employ also deep roentgen-ray therapy to affect the cancer cells lying beyond the effective reach of the radium, but even this combination must be classed generally as palliative rather than curative. In clearly operable cases, that is, in those early cases apparently still confined to the uterus, Crossen feels that immediate removal of the uterus and adjacent tissue likely to be involved is the safest plan. Theoretically we should be able to cure these patients with radium with as great certainty and with far less danger than with the knife; but so far the actual results in cancer of the uterus do not justify displacement of the knife by radium in these early cases. In something over one thousand collected cases of carcinoma of the cervix treated by radium five years previous to the reports, about 20 per cent were cured—approximately the same percentage as by radical operation. When the cases were divided into classes it was found that more of the advanced and borderline cases were cured by radium than by operation, while of the early operable cases the percentage of cures by radium (31 per cent) fell decidedly below that by operation (40 to 45 per cent). We know what can be done with the knife in the individual case but we do not know the extent of the effectiveness of radium in an individual case until it is tried in that case and in the time required for trial by radium the chance of cure by operation slips away. In order to give the patient the best chance of cure in these early cases, it is advisabie to employ both radium and operation. First give a heavy dose of radium, the same as though depending on it to effect a cure, then within a week or ten days do the

radical operation. The operation should be carried out within a short time after the radium treatment because later the radium treatment may have caused such marked connective tissue changes as to increase very decidedly the difficulties and hazard of the operation. This plan of treatment for the early case is based on the assumption that the patient is a good operative risk. If the patient has some serious complication making her a poor operative risk, then her best chance of survival cancer-free may be through radium without operation. The decision for or against operation and of the extent of operation, turns on a balancing of the hazards pro and con—the hazard of operation, the chance of failure of radium to kill the cancer cells in that individual, and the chance of metastasis near and far. On account of the latter danger, it is advisable to supplement the other treatment by deep roentgen-ray treatment.

Urethral Stricture in Women.—Stricture of the urethra in women is a condition which is very often overlooked, according to STEVENS (*Cal. State Jour. Med.*, 1922, **20**, 51) although it may be responsible for marked functional and organic disturbances in the genito-urinary tract in this sex. It is a generally accepted idea that strictures of the female urethra are very uncommon. While this is true so far as the lumen of the canal is concerned, strictures at the meatus on the other hand are frequently encountered. As the female bladder is especially sensitive to reflex influences, marked subjective symptoms are often produced by comparatively slight obstructions. It must be remembered however, that these symptoms may be partly due to the accompanying urethritis or trigonitis. Frequent urination is the most common symptom of which these patients complain. The next most common symptom is pain which is referred to the urethral or bladder regions. The diagnosis is best made by means of the olive-tipped bougie. The majority of these strictures should be treated by means of gradual dilatation, absorption of the constricting exudate being best promoted by this procedure. In the presence of scar tissue however, meatotomy, internal urethrotomy, or external urethrotomy with resection of the scar tissue is often indicated. The symptoms improve, as a rule after two and disappear after five dilatations, recurrence being very unusual if treatment is not too abruptly discontinued.

This subject has also been carefully presented by WYNNE (*Surg. Gynec. and Obst.*, 1922, **34**, 208), who states that the great majority of strictures are single, although multiple ones have been reported; and although the stricture may be located in any part of the urethra, the external meatus and anterior portion are the favorite sites. He classifies strictures as traumatic, inflammatory, neoplastic, congenital, senile and unknown, which terms are self-explanatory. The onset is usually gradual and the course progressive. In some cases the only symptoms noted by the patient are the small stream voided and the length of time required for the act of voiding, but in the great majority of cases there is also some degree of dysuria. The diagnosis is made by examination with sounds or, preferably, olive-tipped or bulbed bougies as advised above by Stevens. In certain cases the strictured area can be felt through the vagina. The endoscope is necessary for a complete examination. Wynne treats these patients by gradual dilatation of the

stricture with sounds, bougies, or Hegar dilators over a considerable period of time. This operation is carried out after a local anesthetic has been applied to the urethral mucous membrane. The dilating instruments should be generously lubricated before insertion and the largest instrument passed at any sitting should be left in place for from ten to fifteen minutes. The size of the dilators used must be determined each time by the degree of pain caused. It is necessary to avoid any severe pain when the treatments are so frequently repeated, as well as to avoid considerable trauma. At first daily treatments are given, but later the intervals between sittings can be increased, and the treatments should be continued over a period of several months. These patients ought to be warned that recurrences are common, and that for this reason they are to return several times a year for dilatation.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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On the Claim that Some Typhoid-Paratyphoid Strains Survive the Milk Pasteurization.—KRUMWIEDE and NOBLE (*Jour. Infect. Dis.*, 1921, **29**, 310) found that "there is no evidence that bacilli of the typhoid and paratyphoid group even in small numbers, will survive heating to 60° C., for twenty minutes," suggesting that the apparent heat resistance of the strains reported by TWISS (*Jour. Infect. Dis.*, 1920, **26**, 165) was due to the test method employed, namely, the use of cotton plugged flasks submerged to twice the depths of the milk. The authors used 27 typhoid cultures recently isolated from carriers, 7 paratyphoid A, 12 paratyphoid B and 4 enteritidis cultures. Milk was sterilized and 100 cc of it was infected with the cultural growth from two twenty-four hour agar slants suspended in salt solution. The bacterial suspension was added after the milk had reached 60° C., rubber stoppers were inserted, the bottles vigorously shaken and completely submerged in a water bath for fifteen minutes. No bacteria survived a pasteurization period thus limited closely to fifteen minutes at 60° C.

Antirabic Vaccination by Means of Desiccated Virus.—With slight modifications, D'AUNOY (*Jour. Infect. Dis.*, 1921, **29**, 261) has employed a desiccated virus prepared according to Harris on account of its capability of production in a short time and preservation over indefinite periods. Full grown, healthy rabbits, averaging 2200 gm. were inoculated into the lateral ventricles after trephining with about 0.004 mg.

of desiccated fixed virus in 1 cc of sterile salt solution. The animal developed symptoms in six or seven days and when complete paresis had intervened, was killed by ether narcosis. The cord and brain were then removed aseptically, and the membranes were stripped off by needles. By grinding with salt solution, the nerve tissue was brought to a coarse paste in a mortar. Carbon dioxide snow was then added with constant mixing and triturating until the mass had solidified. The mass was then placed in a meat grinder and kept at a temperature of about 12° C. for a few hours, a small amount of CO_2 again added and quick grinding accomplished. The ground material was spread in a thin layer and dried in a Scheibler desiccator at from 12 to 18° C. With a vacuum of 2 mm of mercury, and phosphoric anhydride, complete desiccation was procured in about thirty-six hours. The dried virus was kept in large glass tubes in a dark place at from 10 to 15° C. Control cultures of every batch of virus were instituted. The unit or "minimal infective dose" consists of the least amount of virus which within five days after preparation will cause paresis in a 2400 gm. rabbit on the seventh day following intracerebral injection. A virus containing 300 to 500 "minimal infective doses" per mg. was readily produced. It will lose no infectivity at 10° C. for over two years and will last about three years at 8 to 12° C. Adults were given 11 treatments of a total of 17,750 "minimal infective doses" except in severe head injuries when 15 treatments of a total of 25,750 m. i. d. were administered subcutaneously. Only 1 death following complete treatment is reported in 1538 treated patients; 697 injuries by animals proved to be rabid. No paralysis or other untoward effects were encountered in the treated persons. The author feels that his results "on the basis of comparison with similar reports on the use of the original Pasteur dried cord method, argue for the efficaciousness and safety of the desiccated virus method of prophylactic antirabic vaccination."

Botulism from Cheese.—Evidence that botulism is widely disseminated in this country can be found in the sporadic reports which have appeared in recent years. Although it was once thought that the botulinus toxin was produced only in the presence of meat protein, Dickson was able to find it in the presence of vegetable protein and now NEVIN (*Jour. Inf. Dis.*, 1921, **27**, 226) reports the recovery of both B. botulinus and its toxin from home-made cottage cheese, after the ingestion of which three persons died. Two cases presented paralysis of the muscles of deglutition, suffusion of the face, ptosis, total dilatation and failure of the pupils to react to light and paralysis of the muscles of the throat with difficulty of speech. The third patient was unable to swallow. There was no loss of consciousness or paresis of any other part of the body. Subcutaneous inoculation of 3 cc of an emulsion of the cheese, after forty-eight hours' incubation at 37° C., killed guinea-pigs within thirty-six hours. By anaërobic methods, a Gram-positive, motile, oval, sporebearing bacillus was isolated. No capsule could be demonstrated, gelatin was liquefied slowly and milk coagulated in three days. Many carbohydrates were fermented with the production of gas and the odor of butyric acid. A potent toxin was produced on a peptone-free medium. Guinea-pigs

were killed in four days with 0.0005 cc of the filtrate of a seventy-two hour culture. A protective serum was produced in rabbits against the homologous toxin. The author states that this is the first time that B. botulinus has been isolated from cheese, that a soluble bacterial toxin has been detected in cheese and that B. botulinus has been isolated in America.

Studies on the Chemotherapy of the Experimental Typhoid Carrier Condition.—Appreciating the menace of typhoid carriers to society and conceiving the probability that certain anilin derivatives may be toxic to the typhoid bacillus in vivo, BECKWITH (*Jour. Infect. Dis.*, 1921, **29**, 495) administered auramine, acriflavin, proflavine, pyronine G and new fast-green 3 B—all of which showed bactericidal action in bile and serum—intravenously into rabbits in which the typhoid carrier state had been produced by the Gay-Claypole technic. It was found that acriflavine and proflavine were more germicidal in the presence of serum than in its absence, while bile usually depressed the activity of the stains as much as serum. All the stains save new fast-green 3 B, although bactericidal to B. typhosus in vitro, did not sterilize the gall-bladders when introduced intravenously. Auramine was too toxic and the others were excreted through the urine rather than the bile. The writer believes that new fast-green 3 B "offers possibilities as a germicide in vivo for B. typhosus in gall-bladders of experimental rabbit carriers," inasmuch as it retains its activity in serum and bile and is excreted through the bile when administered intravenously, although it does not clear up the condition in all animals. The dye changes readily from the sol to the gel state and may be very toxic to the animal.

Comparison of Formol and Wassermann Reactions in Diagnosis of Syphilis.—Following the report of Gaté and Papacostas, that pooled syphilitic serum was coagulated by a small quantity of formalin, while nonsyphilitic serum failed to give the reaction, ECKER (*Jour. Infect. Dis.*, 1921, **29**, 359) conducted 500 comparative tests, employing the ice-box method for the Wassermann reaction with syphilitic fetal liver, normal human and beef-heart antigens. The technic of "formol" method consisted in adding two drops of Schering's or C. P. formalin, in both acid and neutralized solution, to 1 cc of clear serum, shaking gently in tubes plugged with cotton or more tightly and incubating for from twenty-four to forty-eight hours at temperatures of either ice-box, room or 37° C. Whereas, in a series of 400 comparative tests Gaté and Papacostas found agreement in 85 per cent, only 37.09 per cent of the total number of positive reactions agreed in the writer's series, which compared more closely with the 27.27 per cent as found in a similar work by Pauzot. Forty-four per cent of the formol positives were of the + type, and of these, 13 were positive by the Wassermann. The writer concludes that "the reaction as it stands is of no diagnostic value because of its failure to react in clinically and serologically clear-cut cases of syphilis and the occurrence of positive reaction in the absence of the disease."

HYGIENE AND PUBLIC HEALTH

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Tuberculosis of Husband and Wife.—BARNES (*Am. Rev. Tuberc.*, 1921, **5**, 670) states that the histories of 229 consecutive widowed patients admitted to the Rhode Island State Sanatorium, 1905 to 1921, show that 93, or 40 per cent, lost their consorts by death from tuberculosis, a tuberculosis mortality over three times that of the married people of the community. Immunity from many diseases is short-lived and until much more convincing evidence of permanent immunity against tuberculosis conferred by childhood infections is forthcoming, a cautious logic will not accept the confident statements that are being made as to the impossibility or rarity of adult infection.

The Etiology of Typhus Fever.—The past twelve years have witnessed an energetic investigation into the precise nature of the virus of typhus fever. A number of bacteria have been brought forward as causal agents of the disease. Two of these attracted special attention; namely, *Rickettsia prowazecki* of da Rocha-Lima and *B. typhi exanthematici* of Plotz. Several years ago, OLITSKY (*Jour. Infect. Dis.*, 1916, **19**, 811) was led to accept the etiological relationship of Plotz's bacillus to typhus fever by the fact that he found specific antibodies against the organism in the blood of typhus patients; that with it, it was believed, experimental typhus in guinea-pigs had been induced and that a similar bacterium was recovered from typhus-infected lice. Olitsky (*Jour. Exp. Med.*, 1921, **34**, 525) revises his judgment concerning Plotz's bacillus, for he finds that in the early stages of typhus fever in guinea-pigs the typhus virus can be obtained wholly free from admixture with any of the ordinary bacteria. Furthermore, the body of the guinea-pig reacting to the virus of typhus fever is readily invaded by a variety of bacteria whose presence complicates the typhus infection, but which have no etiological relation to the specific disease, typhus fever. Olitsky showed that during the period of incubation and before the onset of fever no ordinary bacteria appear in the cultures, while on the first day of the febrile reaction different bacteria were found in 6 of 26 guinea-pigs cultured; on the second day, in 10 of 16; on the third day, in 3 of 4; and on the fourth day in cultures of all of the 4 guinea-pigs observed. The findings indicate that the virus of typhus fever is distinct from ordinary cultivable bacteria, and, as the disease set up by the virus progresses, the infected guinea-pigs become subject to

invasion by secondary or concurrent bacteria which thus induce a mixed infection. The bacteria which under the influence of the virus of typhus fever thus invade the body of the guinea-pig are of several kinds, and vary not only among themselves, but also with the day of the fever on which the examination is made. Thus, on the first day of the fever, Plotz's bacilli were recovered twice and anaërobic streptococci, *proteus* bacilli, aërobic diphtheroids, Gaertner type bacilli, and *Staphylococcus aureus*, each once. On the second day Plotz's bacilli were found four times, anaërobic streptococci three times, Gaertner type bacilli, aërobic diphtheroids, *Bacillus welchii*, aërobic Gram-positive diplobacilli, and *Staphylococcus aureus*, each once. On the third day Plotz's bacilli were recovered once, as were anaërobic streptococci and Gaertner type bacilli. On the fourth day, *Staphylococcus aureus* was found twice and Plotz's bacilli and *Bacillus proteus* each once. The variation in the kind of bacteria, as well as the lack of predominance of one kind over another during the different stages of the febrile reaction in guinea-pigs, led Olitsky to infer that they occur concurrently with the typhus virus. And since the more unusual of these organisms, the Plotz bacillus, the anaërobic streptococcus, the aërobic diphtheroid, and the diplobacillus are non-pathogenic for guinea-pigs, while the more common bacteria such as the Gaertner type bacillus, Welch's bacillus, the proteus bacillus, and the staphylococci induce distinctive effects, and since all the bacteria could be suppressed without their reappearance in guinea-pig passages of the virus containing them, Olitsky believes that they are independent and unrelated to the true virus of typhus fever.

Viability of the Colon-typhoid Group in Carbonated Water and Carbonated Beverages.—Koser and Skinner (*Jour. Bact.*, 1922, **1**, 111) found that under the conditions of their experiments carbonation exerted a distinctly harmful effect upon the members of the colon-typhoid group and that their period of viability in carbonated water was much shorter than in plain tap water. The destructive effect of the CO_2 was especially marked at room temperature, 19° to 23° C., and less so at 10° C. The authors state that in a "non-acid" beverage, the organisms may persist for a slightly longer period than in carbonated water. In beverages containing 0.094 per cent or greater amounts of citric or lactic acids, the death-rate is very rapid and is apparently due to the effect of these acids, irrespective of the CO_2. B. Typhosus and B. paratyphosus B are more readily destroyed by CO_2 than is B. coli. The spore forms of a common aërobe, B. mesentericus, and of a common anaërobe, C. sporogenes, were found to be quite resistant to carbonation, surviving one month at room temperature with no apparent diminution in numbers. The authors emphasize the fact that throughout their experiments the water used for carbonation and for preparation of the various beverages was an ordinary city supply of low mineral content. They state that under certain conditions, as for example in carbonated water of high mineral content, it is possible that non-sporeforming organisms may remain alive for longer periods than those reported. This possible influence of certain inorganic salts upon the viability of microörganisms in a carbonated environment has not been studied in the present investigation. The authors state

emphatically that the results obtained in the investigation do not warrant the conclusion that water of a low sanitary quality can be used by the industry in the preparation of carbonated beverages, or that carbonation can be relied upon to destroy evidence of pollution. They state that in many instances, particularly during the summer months, beverages are consumed within a few hours after their preparation and it is obvious that under these conditions pathogenic organisms, if originally present in the water, may survive carbonation and reach the consumer.

Table Utensils as Sources of Tuberculous Infection.—FLOYD and FROTHINGHAM (*Am. Rev. Tuberc.*, 1922, **6**, 51) state that the table utensils used by open consumptives may occasionally harbor virulent tubercle bacilli, even after more careful washing than is customary in the average home. The water used to wash such utensils quite frequently contains virulent tubercle bacilli. Floyd and Frothingham conclude from their experiments that it seems evident that the table utensils used by an open consumptive may be not only a menace to the patient himself and to others in his family, but also a general menace when the patient eats in public places. They state that the inference also seems warranted that the dish towel used to wipe these utensils must become contaminated with virulent tubercle bacilli, and the more frequently it is used the more bacilli accumulate, so that if employed for several days without thorough washing, a common practice in many homes, it becomes more and more a depositor of tubercle on the just washed utensils. It would seem, therefore, that the only way to control the danger of spreading tuberculosis by such utensils is to thoroughly sterilize the patients' tableware and the dish towel employed to wipe it after each meal, and the simplest method to accomplish this is to boil them for several minutes.

The Present-day Sources of Common Salt in Relation to Health and Especially to Iodine Scarcity and Goiter.—HAYHURST (*Jour. Am. Med. Ass.*, 1922, **78**, 18) states that while iodine may occur in natural deposits along with chlorine, usually in the form of the sodium salt, it is never obtained from such sources commercially because it occurs in too limited quantities. Chili saltpeter is the chief source of iodine. The sea is the great storehouse of iodine where it completes a cycle from inorganic compounds to organic life and return. The salts of sea water are constant in both quality and quantity. Sodium chloride comprises 77.8 per cent, magnesium chloride 10.9 per cent with many other compounds, including sodium iodide, composing the remaining 11.3 per cent. It has an average total salinity of 3.4404 per cent. All of the salts in sea water are unusually soluble in plain water. The great solubility of sodium iodide accounts for its almost complete absence from the land surface and, perhaps, for some of the peculiarities noted in regard to the incidence of goiter. Authorities are agreed that goiter is infrequent in both animals and man along the sea. The same is true also of some fish (salmons) which inhabit both fresh water and sea water, tending to develop goiters in the former, and none in the latter. Apparently sea animals do not have goiter. Practically all salt used in the United States for dietary consumption is obtained from inland sources by the

evaporation of brines, which for the most part are inherently free of iodine. Irrespective of the source, whether sea water or inland deposits, the modern processes of preparing and purifying salt free it from all traces of iodine, as well as its other naturally associated elements, many of which are identical with the body fluids of higher animals. Hayhurst concludes that an analogy should be drawn from sea life and a precept taken from evolution. Of the dependable source of iodine in Nature—sea air, sea food and sea water—it is to sea water, used perhaps in place of common salt as a condiment, that inland dwellers should look. This substitution would appear to offer a complete solution to the iodine deficiency problem, if nothing else; while evidence would tend to show that other constituents of sea water have also an undoubted place in the economy of the higher animal organism, perhaps to the extent of precluding some diseases which are likewise possibly of a deficiency type. Common salt for dietary purposes should include not only sodium chloride but also sodium iodide, and undoubtedly many of its other original concomitants. For geochemical reasons, great care should be taken in selecting its source, if it is not actually derived always from sea water. It must then be handled commercially in a manner to retain these constituents.

The Destruction of Tubercle Bacilli in Sewage by Chlorine.—Conroy, Conroy and Laird (*Am. Rev. Tuberc.*, 1922, **6**, 63) state that sewage from a tuberculosis sanatorium nearly always contains living tubercle bacilli. The use of a chlorine machine is a practical means of ridding such sewage of tubercle bacilli. Two machines should be used to insure continuous disinfection. Preliminary treatment of the sewage is necessary to reduce it to a liquid form, and to prevent the floating of solid particles containing tubercle bacilli in water courses.

Adequate Industrial Medical Service for the Small Plant.—McCord and Minster (*Jour. Indust. Hyg.*, 1922, **3**, 363) state that the number of workers employed in small factories exceeds the number engaged in work in plants of 500 or more employes. Proportionately, work conditions are less satisfactory in small factories than in larger plants. It is desirable that some means be found to apply to the small plant the same type of health conservation measures that have proved so successful and so valuable in larger plants. The experience of a group of industrial health workers in a small plant averaging one hundred and fifteen employes is recorded. The results of such work have been of sufficient benefit to justify the assertion that this procedure may successfully be applied to small plants in general.

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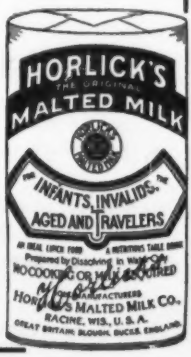

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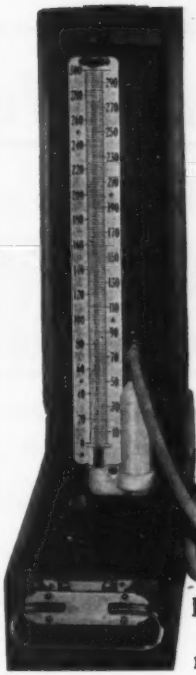

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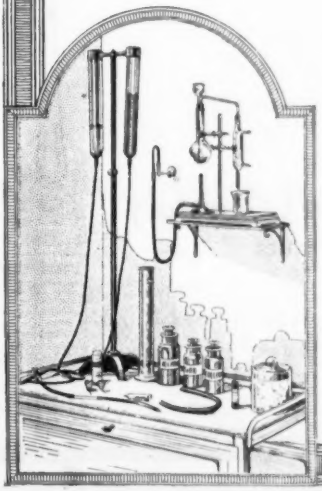

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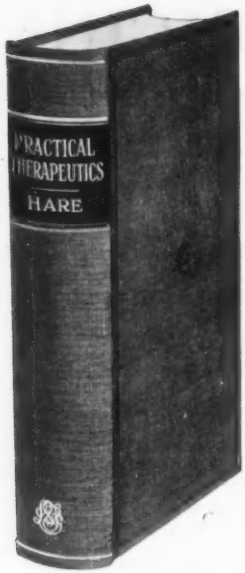

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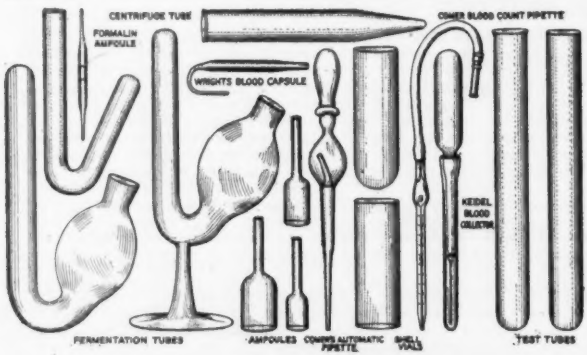

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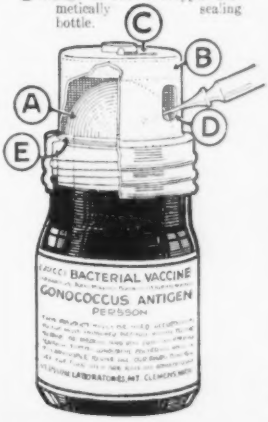

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